

Sandostatin LAR® Depot

(octreotide acetate for injectable suspension)

Rx only

Prescribing Information

DESCRIPTION

Octreotide is the acetate salt of a cyclic octapeptide. It is a long-acting octapeptide with pharmacologic properties mimicking those of the natural hormone somatostatin.

Octreotide is known chemically as L-Cysteinamide, D-phenylalanyl-L-cysteiny-L-phenylalanyl-D-tryptophyl-L-tyryl-L-threonyl-N-[2-hydroxy-1-(hydroxy-methyl) propyl]-, cyclic (2→7)-disulfide; [R-(R*,R*)].

Sandostatin LAR® Depot (octreotide acetate for injectable suspension) is available in a vial containing the sterile drug product, which when mixed with diluent, becomes a suspension that is given as a monthly intragluteal injection. The octreotide is uniformly distributed within the microspheres which are made of a biodegradable glucose star polymer, D,L-lactic and glycolic acids copolymer. Sterile mannitol is added to the microspheres to improve suspendability.

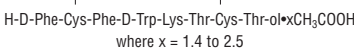
Sandostatin LAR® Depot is available as: sterile 5-mL vials in 3 strengths delivering 10 mg, 20 mg or 30 mg octreotide free peptide. Each vial of Sandostatin LAR® Depot delivers:

Name of Ingredient	10 mg	20 mg	30 mg
octreotide acetate	11.2 mg*	22.4 mg*	33.6 mg*
D, L-lactic and glycolic acids copolymer	188.8 mg	377.6 mg	566.4 mg
mannitol	41.0 mg	81.9 mg	122.9 mg
*Equivalent to 10/20/30 mg octreotide base.			

Each syringe of diluent contains:

carboxymethylcellulose sodium	12.5 mg
mannitol	15.0 mg
water for injection	2.5 mL

The molecular weight of octreotide is 1019.3 (free peptide, C₄₉H₆₆N₁₀O₁₀S₂) and its amino acid sequence is



CLINICAL PHARMACOLOGY

Sandostatin LAR® Depot (octreotide acetate for injectable suspension) is a long-acting dosage form consisting of microspheres of the biodegradable glucose star polymer, D,L-lactic and glycolic acids copolymer, containing octreotide. It maintains all of the clinical and pharmacological characteristics of the immediate-release dosage form Sandostatin® (octreotide acetate) Injection with the added feature of slow release of octreotide from the site of injection, reducing the need for frequent administration. This slow release occurs as the polymer biodegrades, primarily through hydrolysis.

Sandostatin LAR® Depot is designed to be injected intramuscularly (intragluteally) once every four weeks.

Octreotide exerts pharmacologic actions similar to the natural hormone, somatostatin. It is an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin, it also suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.

By virtue of these pharmacological actions, octreotide has been used to treat the symptoms associated with metastatic carcinoid tumors (flushing and diarrhea), and Vasoactive Intestinal Peptide (VIP) secreting adenomas (watery diarrhea).

Octreotide substantially reduces and in many cases can normalize growth hormone and/or IGF-1 (somatomedin C) levels in patients with acromegaly.

Single doses of Sandostatin® Injection given subcutaneously have been shown to inhibit gallbladder contractility and to decrease bile secretion in normal volunteers. In controlled clinical trials the incidence of gallstone or biliary sludge formation was markedly increased (see WARNINGS).

Octreotide may cause clinically significant suppression of thyroid stimulating hormone (TSH).

Pharmacokinetics

The magnitude and duration of octreotide serum concentrations after an intramuscular injection of the long-acting depot formulation Sandostatin LAR® Depot reflect the release of drug from the microsphere polymer matrix. Drug release is governed by the slow biodegradation of the microspheres in the muscle, but once present in the systemic circulation, octreotide distributes and is eliminated according to its known pharmacokinetic properties which are as follows:

1. Pharmacokinetics of Octreotide Acetate

According to data obtained with the immediate-release formulation, Sandostatin® Injection solution, after subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.2 ng/mL (100 mcg dose) were reached 0.4 hours after dosing. Using a specific radioimmunoassay, intravenous and subcutaneous doses were found to be bioequivalent. Peak concentrations and area-under-the-curve values were dose proportional both after subcutaneous or intravenous single doses up to 400 mcg and with multiple doses of 200 mcg t.i.d. (600 mcg/day). Clearance was reduced by about 66% suggesting non-linear kinetics of the drug at daily doses of 600 mcg/day as compared to 150 mcg/day. The relative decrease in clearance with doses above 600 mcg/day is not defined.

In healthy volunteers the distribution of octreotide from plasma was rapid ($t_{\alpha,1/2}$ = 0.2 h), the volume of distribution (Vdss) was estimated to be 13.6 L and the total body clearance was 10 L/h.

In blood, the distribution of octreotide into the erythrocytes was found to be negligible and about 65% was bound in the plasma in a concentration-independent manner. Binding was mainly to lipoprotein and, to a lesser extent, to albumin.

The elimination of octreotide from plasma had an apparent half-life of 1.7 hours, compared with the 1-3 minutes with the natural hormone, somatostatin. The duration of action of subcutaneously administered Sandostatin® Injection solution is variable but extends up to 12 hours depending upon the type of tumor, necessitating multiple daily dosing with this immediate-release dosage form. About 32% of the dose is excreted unchanged into the urine. In an elderly population, dose adjustments may be necessary due to a significant increase in the half-life (46%) and a significant decrease in the clearance (26%) of the drug.

In patients with acromegaly, the pharmacokinetics differ somewhat from those in healthy volunteers. A mean peak concentration of 2.8 ng/mL (100 mcg dose) was reached in 0.7 hours after subcutaneous dosing. The volume of distribution (Vdss) was estimated to be 21.6 ± 8.5 L and the total body clearance was increased to 18 L/h. The mean percent of the drug bound was 41.2%. The disposition and elimination half-lives were similar to normals.

In patients with severe renal failure requiring dialysis, clearance was reduced to about half that found in healthy subjects (from approximately 10 L/h to 4.5 L/h).

The effect of hepatic diseases on the disposition of octreotide is unknown.

2. Pharmacokinetics of Sandostatin LAR® Depot

After a single IM injection of the long-acting depot dosage form Sandostatin LAR® Depot in healthy volunteer subjects, the serum octreotide concentration reached a transient initial peak of about 0.03 ng/mL/mg within 1 hour after administration progressively declining over the following 3 to 5 days to a nadir of <0.01 ng/mL/mg, then slowly increasing and reaching a plateau about two to three weeks post injection. Plateau concentrations were maintained over a period of nearly 2-3 weeks, showing dose proportional peak concentrations of about 0.07 ng/mL/mg. After about 6 weeks post injection, octreotide concentration slowly decreased, to <0.01 ng/mL/mg by weeks 12 to 13, concomitant with the terminal degradation phase of the polymer matrix of the dosage form. The relative bioavailability of the long-acting release Sandostatin LAR® Depot compared to immediate-release Sandostatin® Injection solution given subcutaneously was 60%-63%.

In patients with acromegaly, the octreotide concentrations after single doses of 10 mg, 20 mg and 30 mg Sandostatin LAR® Depot were dose proportional. The transient day 1 peak, amounting to 0.3 ng/mL, 0.8 ng/mL, and 1.3 ng/mL, respectively, was followed by plateau concentrations of 0.5 ng/mL, 1.3 ng/mL, and 2.0 ng/mL, respectively, achieved about 3 weeks post injection. These plateau concentrations were maintained for nearly two weeks.

Following multiple doses of Sandostatin LAR® Depot given every 4 weeks, steady-state octreotide serum concentrations were achieved after the third injection. Concentrations were dose proportional and higher by a factor of approximately 1.6 to 2.0 compared to the concentrations after a single dose. The steady-state octreotide concentrations were 1.2 ng/mL and 2.1 ng/mL, respectively, at trough and 1.6 ng/mL and 2.6 ng/mL, respectively, at peak with 20 mg and 30 mg Sandostatin LAR® Depot given every 4 weeks. No accumulation of octreotide beyond that expected from the overlapping release profiles occurred over a duration of up to 28 monthly injections of Sandostatin LAR® Depot. With the long-acting depot formulation Sandostatin LAR® Depot administered IM every 4 weeks the peak-to-trough variation in octreotide concentrations ranged from 44%-68%, compared to the 163%-209% variation encountered with the daily subcutaneous t.i.d. regimen of Sandostatin® Injection solution.

In patients with carcinoid tumors, the mean octreotide concentrations after 6 doses of 10 mg, 20 mg and 30 mg Sandostatin LAR® Depot administered by IM injection every four weeks were 1.2 ng/mL, 2.5 ng/mL, and 4.2 ng/mL, respectively. Concentrations were dose proportional and steady-state concentrations were reached after two injections of 20 mg and 30 mg and after three injections of 10 mg.

Sandostatin LAR® Depot has not been studied in patients with renal impairment.

Sandostatin LAR® Depot has not been studied in patients with hepatic impairment.

CLINICAL TRIALS

The clinical trials of Sandostatin LAR® Depot (octreotide acetate for injectable suspension) were performed in patients who had been receiving Sandostatin® (octreotide acetate) Injection for a period of weeks to as long as 10 years. The acromegaly studies with Sandostatin LAR® Depot described below were performed in patients who achieved GH levels of <10 ng/mL (and, in most cases <5 ng/mL) while on subcutaneous Sandostatin® Injection. However, some patients enrolled were partial responders to subcutaneous Sandostatin® Injection, i.e., GH levels were reduced by >50% on subcutaneous Sandostatin® Injection compared to the untreated state, although not suppressed to <5 ng/mL.

Acromegaly

Sandostatin LAR® Depot was evaluated in three clinical trials in acromegalic patients.

In two of the clinical trials, a total of 101 patients were entered who had, in most cases, achieved a GH level <5 ng/mL on Sandostatin® Injection given in doses of 100 mcg or 200 mcg t.i.d. Most patients were switched to 20 mg or 30 mg doses of Sandostatin LAR® Depot given once every 4 weeks for up to 27 to 28 injections. A few patients received doses of 10 mg and a few required doses of 40 mg. Growth hormone and IGF-1 levels were at least as well controlled with Sandostatin LAR® Depot as they had been on Sandostatin® Injection and this level of control remained for the entire duration of the trials.

A third trial was a 12-month study that enrolled 151 patients who had a GH level <10 ng/mL after treatment with Sandostatin® Injection (most had levels <5 ng/mL). The starting dose of Sandostatin LAR® Depot was 20 mg every 4 weeks for 3 doses. Thereafter, patients received 10 mg, 20 mg or 30 mg every 4 weeks, depending upon the degree of GH suppression. (The recommended regimen for these dosage changes is described under DOSAGE AND ADMINISTRATION.) Growth hormone and IGF-1 were at least as well controlled on Sandostatin LAR® Depot as they had been on Sandostatin® Injection.

Table 1 summarizes the data on hormonal control (GH and IGF-1) for those patients in the first two clinical trials who received all 27 to 28 injections of Sandostatin LAR® Depot.

Mean Hormone Level	Sandostatin® Injection S.C.		Sandostatin LAR® Depot	
	N	%	N	%
GH <5.0 ng/mL	69/88	78	73/88	83
<2.5 ng/mL	44/88	50	41/88	47
<1.0 ng/mL	6/88	7	10/88	11
IGF-1 normalized	36/88	41	45/88	51
GH <5.0 ng/mL + IGF-1 normalized	36/88	41	45/88	51
<2.5 ng/mL + IGF-1 normalized	30/88	34	37/88	42
<1.0 ng/mL + IGF-1 normalized	5/88	6	10/88	11

¹ Average of monthly levels of GH and IGF-1 over the course of the trials

For the 88 patients in Table 1, a mean GH level of <2.5 ng/mL was observed in 47% receiving Sandostatin LAR® Depot. Over the course of the trials 42% of patients maintained mean growth hormone levels of <2.5 ng/mL and mean normal IGF-1 levels.

Table 2 summarizes the data on hormonal control (GH and IGF-1) for those patients in the third clinical trial who received all 12 injections of Sandostatin LAR® Depot.

Mean Hormone Level	Sandostatin® Injection S.C.		Sandostatin LAR® Depot	
	N	%	N	%
GH <5.0 ng/mL	116/122	95	118/122	97
<2.5 ng/mL	84/122	69	80/122	66
<1.0 ng/mL	25/122	21	28/122	23
IGF-1 normalized	82/122	67	82/122	67
GH <5.0 ng/mL + IGF-1 normalized	80/122	66	82/122	67
<2.5 ng/mL + IGF-1 normalized	65/122	53	70/122	57
<1.0 ng/mL + IGF-1 normalized	23/122	19	27/122	22

¹ Average of monthly levels of GH and IGF-1 over the course of the trial

For the 122 patients in Table 2, who received all 12 injections in the third trial, a mean GH level of <2.5 ng/mL was observed in 66% receiving Sandostatin LAR® Depot. Over the course of the trial 57% of patients maintained mean growth hormone levels of <2.5 ng/mL and mean normal IGF-1 levels. In comparing the hormonal response in these trials, note that a higher percentage of patients in the third trial suppressed their mean GH to <5 ng/mL on subcutaneous Sandostatin® Injection, 95%, compared to 78% across the two previous trials.

In all three trials, GH, IGF-1, and clinical symptoms were similarly controlled on Sandostatin LAR® Depot as they had been on Sandostatin® Injection.

Of the 25 patients who completed the trials and were partial responders to Sandostatin® Injection (GH >5.0 ng/mL but reduced by >50% relative to untreated levels), 1 patient (4%) responded to Sandostatin LAR® Depot with a reduction of GH to <2.5 ng/mL and 8 patients (32%) responded with a reduction of GH to <5.0 ng/mL.

Carcinoid Syndrome

A 6-month clinical trial of malignant carcinoid syndrome was performed in 93 patients who had previously been shown to be responsive to Sandostatin® Injection. Sixty-seven patients were randomized at baseline to receive, double-blind, doses of 10 mg, 20 mg or 30 mg Sandostatin LAR® Depot every 28 days and 26 patients continued, unblinded, on their previous Sandostatin® Injection regimen (100-300 mcg t.i.d.).

In any given month after steady-state levels of octreotide were reached, approximately 35%-40% of the patients who received Sandostatin LAR® Depot required supplemental subcutaneous Sandostatin® Injection therapy usually for a few days, to control exacerbation of carcinoid symptoms. In any given month the percentage of patients randomized to subcutaneous Sandostatin® Injection, who required supplemental treatment with an increased dose of Sandostatin® Injection, was similar to the percentage of patients randomized to Sandostatin LAR® Depot. Over the six-month treatment period approximately 50%-70% of patients who completed the trial on Sandostatin LAR® Depot required subcutaneous Sandostatin® Injection supplemental therapy to control exacerbation of carcinoid symptoms although steady-state serum Sandostatin LAR® Depot levels had been reached.

Table 3 presents the average number of daily stools and flushing episodes in malignant carcinoid patients.

Treatment	N	Daily Stools (Average No.)		Daily Flushing Episodes (Average No.)	
		Baseline	Last Visit	Baseline	Last Visit
Sandostatin® Injection S.C.	26	3.7	2.6	3.0	0.5
Sandostatin LAR® Depot					
10 mg	22	4.6	2.8	3.0	0.9
20 mg	20	4.0	2.1	5.9	0.6
30 mg	24	4.9	2.8	6.1	1.0

Overall, mean daily stool frequency was as well controlled on Sandostatin LAR® Depot as on Sandostatin® Injection (approximately 2 to 2.5 stools/day).

Mean daily flushing episodes were similar at all doses of Sandostatin LAR® Depot and on Sandostatin® Injection (approximately 0.5 to 1 episode/day).

In a subset of patients with variable severity of disease, median 24 hour urinary 5-HIAA (5-hydroxyindole acetic acid) levels were reduced by 38%-50% in the groups randomized to Sandostatin LAR® Depot.

The reductions are within the range reported in the published literature for patients treated with octreotide (about 10%-50%).

Seventy-eight patients with malignant carcinoid syndrome who had participated in this 6-month trial, subsequently participated in a 12-month extension study in which they received 12 injections of Sandostatin LAR® Depot at 4-week intervals. For those who remained in the extension trial, diarrhea and flushing were as well controlled as during the 6-month trial. Because malignant carcinoid disease is progressive, as expected, a number of deaths (8 patients: 10%) occurred due to disease progression or complications from the underlying disease. An additional 22% of patients prematurely discontinued Sandostatin LAR® Depot due to disease progression or worsening of carcinoid symptoms.

INDICATIONS AND USAGE

Acromegaly

Sandostatin LAR® Depot (octreotide acetate for injectable suspension) is indicated 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 Sandostatin® (octreotide acetate) Injection. The goal of treatment in acromegaly is to reduce GH and IGF-1 levels to normal. Sandostatin LAR® Depot can be used in patients who have had an inadequate response to surgery or in those for whom surgical resection is not an option. It may also be used in patients who have received radiation and have had an inadequate therapeutic response (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

Carcinoid Tumors

Sandostatin LAR® Depot is indicated for long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors in patients in whom initial treatment with Sandostatin® Injection has been shown to be effective and tolerated.

Vasoactive Intestinal Peptide Tumors (VIPomas)

Sandostatin LAR® Depot is indicated for long-term treatment of the profuse watery diarrhea associated with VIP-secreting tumors in patients in whom initial treatment with Sandostatin® Injection has been shown to be effective and tolerated.

In patients with acromegaly, carcinoid syndrome and VIPomas, the effect of Sandostatin® Injection and Sandostatin LAR® Depot on tumor size, rate of growth and development of metastases, has not been determined.

CONTRAINDICATIONS

Sensitivity to this drug or any of its components.

WARNINGS

Adverse events that have been reported in patients receiving Sandostatin® (octreotide acetate) Injection can also be expected in patients receiving Sandostatin LAR® Depot (octreotide acetate for injectable suspension). Incidence figures in the WARNINGS and ADVERSE REACTIONS sections, below, are those obtained in clinical trials of Sandostatin® Injection and Sandostatin LAR® Depot.

Gallbladder and Related Events

Single doses of Sandostatin® Injection have been shown to inhibit gallbladder contractility and decrease bile secretion in normal volunteers. In clinical trials with Sandostatin® Injection (primarily patients with acromegaly or psoriasis) in patients who had not previously received octreotide, the incidence of biliary tract abnormalities was 63% (27% gallstones, 24% sludge without stones, 12% biliary duct dilatation). The incidence of stones or sludge in patients who received Sandostatin® Injection for 12 months or longer was 52%. The incidence of gallbladder abnormalities did not appear to be related to age, sex or dose but was related to duration of exposure.

In clinical trials 52% of acromegalic patients, most of whom received Sandostatin LAR® Depot for 12 months or longer, developed new biliary abnormalities including gallstones, microlithiasis, sediment, sludge and dilatation. The incidence of new cholelithiasis was 22%, of which 7% were microstones.

In clinical trials 62% of malignant carcinoid patients who received Sandostatin LAR® Depot for up to 18 months developed new biliary abnormalities including gallstones, sludge and dilatation. New gallstones occurred in a total of 24% of patients.

Across all trials, a few patients developed acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, or pancreatitis during octreotide therapy or following its withdrawal. One patient developed ascending cholangitis during Sandostatin® Injection therapy and died. Despite the high incidence of new gallstones in patients receiving octreotide, 1% of patients developed acute symptoms requiring cholecystectomy.

PRECAUTIONS (See ADVERSE REACTIONS.)

General

Growth hormone secreting tumors may sometimes expand and cause serious complications (e.g., visual field defects). Therefore, all patients with these tumors should be carefully monitored.

Octreotide alters the balance between the counter-regulatory hormones, insulin, glucagon and growth hormone, which may result in hypoglycemia or hyperglycemia.

Octreotide also suppresses secretion of thyroid stimulating hormone, which may result in hypothyroidism. Cardiac conduction abnormalities have also occurred during treatment with octreotide.

Glucose Metabolism

The hypoglycemia or hyperglycemia which occurs during octreotide therapy is usually mild, but may result in overt diabetes mellitus or necessitate dose changes in insulin or other hypoglycemic agents. Severe hyperglycemia, subsequent pneumonia, and death following initiation of Sandostatin® (octreotide acetate) Injection therapy was reported in one patient with no history of hyperglycemia (see ADVERSE REACTIONS).

In patients with concomitant Type I diabetes mellitus, Sandostatin Injection and Sandostatin LAR® Depot (octreotide acetate for injectable suspension) are likely to affect glucose regulation, and insulin requirements may be reduced. Symptomatic hypoglycemia, which may be severe, has been reported in these patients. In non-diabetics and Type II diabetics with partially intact insulin reserves, Sandostatin Injection or Sandostatin LAR Depot administration may result in decreases in plasma insulin levels and hyperglycemia. It is therefore recommended that glucose tolerance and antidiabetic treatment be periodically monitored during therapy with these drugs.

Thyroid Function

Hypothyroidism has been reported in acromegaly and carcinoid patients receiving octreotide therapy. Baseline and periodic assessment of thyroid function (TSH, total and/or free T₄) is recommended during chronic octreotide therapy (see ADVERSE REACTIONS).

Cardiac Function

In all acromegalic and carcinoid syndrome patients, bradycardia, arrhythmias and conduction abnormalities have been reported during octreotide therapy. Other EKG changes were observed such as QT prolongation, axis shifts, early repolarization, low voltage, R/S transition, early R wave progression, and non-specific ST-T wave changes. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease (see PRECAUTIONS). Dose adjustments in drugs such as beta-blockers that have bradycardia effects may be necessary. In one acromegalic patient with severe congestive heart failure, initiation of Sandostatin® Injection therapy resulted in worsening of CHF with improvement when drug was discontinued. Confirmation of a drug effect was obtained with a positive rechallenge (see ADVERSE REACTIONS).

Nutrition

Octreotide may alter absorption of dietary fats in some patients.

Depressed vitamin B₁₂ levels and abnormal Schilling's tests have been observed in some patients receiving octreotide therapy, and monitoring of vitamin B₁₂ levels is recommended during therapy with Sandostatin LAR® Depot.

Octreotide has been investigated for the reduction of excessive fluid loss from the G.I. tract in patients with conditions producing such a loss. If such patients are receiving total parenteral nutrition (TPN), serum zinc may rise excessively when the fluid loss is reversed. Patients on TPN and octreotide should have periodic monitoring of zinc levels.

Information for Patients

Patients with carcinoid tumors and VIPomas should be advised to adhere closely to their scheduled return visits for reinjection in order to minimize exacerbation of symptoms.

Patients with acromegaly should also be urged to adhere to their return visit schedule to help assure steady control of GH and IGF-1 levels.

Laboratory Tests

Laboratory tests that may be helpful as biochemical markers in determining and following patient response depend on the specific tumor. Based on diagnosis, measurement of the following substances may be useful in monitoring the progress of therapy:

Acromegaly: Growth Hormone, IGF-1 (somatomedin C)

Responsiveness to octreotide may be evaluated by determining growth hormone levels at 1-4 hour intervals for 8-12 hours after subcutaneous injection of Sandostatin® Injection (not Sandostatin LAR® Depot). Alternatively, a single measurement of IGF-1 (somatomedin C) level may be made two weeks after initiation of Sandostatin® Injection or dosage change. After patients are switched from Sandostatin® Injection to Sandostatin LAR® Depot, GH and IGF-1 determinations may be made after 3 monthly injections of Sandostatin LAR® Depot. (Steady-state serum levels of octreotide are reached only after a period of 3 months of monthly injections.) Growth hormone can be determined using the mean of 4 assays taken at 1-hour intervals. Somatomedin C can be determined with a single assay. All GH and IGF-1 determinations should be made 4 weeks after the previous Sandostatin LAR® Depot.

Carcinoid: 5-HIAA (urinary 5-hydroxyindole acetic acid), plasma serotonin, plasma Substance P

VIPoma: VIP (plasma vasoactive intestinal peptide)

Baseline and periodic total and/or free T₄ measurements should be performed during chronic therapy (see PRECAUTIONS - General).

Drug Interactions

Octreotide has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs. Concomitant administration of octreotide injection with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection.

Patients receiving insulin, oral hypoglycemic agents, beta-blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may require dose adjustments of these therapeutic agents.

Concomitant administration of octreotide and bromocriptine increases the availability of bromocriptine. Limited published data indicate that somatostatin analogs might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormones. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g., quindine, terfenadine) should therefore be used with caution.

Drug Laboratory Test Interactions

EXP.
LOT



1027562

Each vial delivers:
octreotide acetate 11.2 mg*
*equivalent to 10 mg octreotide base
Inactive ingredients:
D,L-lactic and glycolic acids copolymer 188.8 mg
mannitol 41.0 mg
FOR INJECTABLE SUSPENSION
STORAGE: Refrigerate at 2 °C - 8 °C
(36 °F - 46 °F). Protect from light.
Manufactured for Novartis Pharmaceuticals
Corporation, East Hanover, NJ 07936
NOVARTIS 85062101

NDC 0078-0340-84



Warning: Rubber stopper contains LATEX.

Rx only

10mg

EXP.
LOT



1027563

Each vial delivers:
octreotide acetate 22.4 mg*
*equivalent to 20 mg octreotide base
Inactive ingredients:
D,L-lactic acid glycolic acid copolymer... 377.6 mg
mannitol 81.9 mg
FOR INJECTABLE SUSPENSION
STORAGE: Refrigerate at 2 °C - 8 °C
(36 °F - 46 °F). Protect from light.
Manufactured for Novartis Pharmaceuticals
Corporation, East Hanover, NJ 07936
NOVARTIS 85962301

NDC 0078-0341-84



Warning: Rubber stopper contains LATEX.

Rx only

20mg

EXP.
LOT



1027564

Each vial delivers:
octreotide acetate 33.6 mg*
*equivalent to 30 mg octreotide base
Inactive ingredients:
D,L-lactic and glycolic acids copolymer 566.4 mg
mannitol 122.9 mg
FOR INJECTABLE SUSPENSION
STORAGE: Refrigerate at 2 °C - 8 °C
(36 °F - 46 °F). Protect from light.
Manufactured for Novartis Pharmaceuticals
Corporation, East Hanover, NJ 07936
NOVARTIS 85062201

NDC 0078-0342-84



Warning: Rubber stopper contains LATEX.

Rx only **30mg**

EXP.
LOT



1027565

Each vial delivers:
octreotide acetate 33.6 mg*
*equivalent to 30 mg octreotide base
Inactive ingredients:
D,L-lactic and glycolic acids copolymer, 566.4 mg
mannitol 122.9 mg
FOR INJECTABLE SUSPENSION

Warning: Rubber stopper contains LATEX.

Manufactured for Novartis Pharmaceuticals
Corporation, East Hanover, NJ 07936
NOVARTIS 85075701

NDC 0078-0340-97

Sandostatin LAR® Depot
DEMONSTRATION VIAL

WARNING: CONTENTS NOT
SUITABLE FOR HUMAN USE.



Black



Black (60%)



Pantone 072 100%



Pantone 072 60%

----- Do not print (For Perforation Only)

Top Section - 072 with knockout

Bottom Section - transparent background

PLEASE PEEL OFF OUTER LAYER
AFTER PRODUCT SUSPENSION

Diluent
for suspension of
Sandostatin LAR[®] Depot

Each syringe contains:
sodium CMC12.5 mg
mannitol15.0 mg
water for injection 2.5 mL

STORAGE: Refrigerate at 2 °C- 8 °C
(36 °F-46 °F). **Rx only**

Manufactured for:
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936 85057801

EXP. 
LOT 

Sandostatin LAR[®] Depot
(octreotide acetate for
injectable suspension)

10 mg

FOR INTRAGLUTEAL INJECTION

Rx only

Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

 **NOVARTIS** ©Novartis
85057801



Black



Black (60%)



Pantone 1385 100%



Pantone 1385 80%

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Bottom Section - transparent background

PLEASE PEEL OFF OUTER LAYER
AFTER PRODUCT SUSPENSION

Diluent
for suspension of
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mannitol15.0 mg
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Manufactured for:
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936 85059001

EXP.

LOT




Sandostatin LAR[®] Depot
(octreotide acetate for
injectable suspension)

20 mg

FOR INTRAGLUTEAL INJECTION

Rx only

Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

 **NOVARTIS** ©Novartis
85059001



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Black (60%)



Pantone 222 100%



Pantone 222 60%

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Bottom Section - transparent background



PLEASE PEEL OFF OUTER LAYER
AFTER PRODUCT SUSPENSION


Diluent
for suspension of
Sandostatin LAR® Depot

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STORAGE: Refrigerate at 2 °C- 8 °C
(36 °F-46 °F). **Rx only**

Manufactured for:
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936 85059101

EXP. 
LOT 




Sandostatin LAR® Depot
(octreotide acetate for
injectable suspension)





30 mg

FOR INTRAGLUTEAL INJECTION

Rx only

Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

 **NOVARTIS** ©Novartis
85059101

-  Black
-  Black (60%)
-  PMS 032
-  PMS 032 (80%)
- Do not print (For Perforation Only)
- Do not print (For Position Only)

Top Section - white background
 Bottom Section - transparent background

PLEASE PEEL OFF OUTER LAYER
 AFTER PRODUCT SUSPENSION

Diluent

DEMONSTRATION ONLY

Each syringe contains:


sodium CMC	12.5 mg
mannitol	15.0 mg
water for injection	2.5 mL

**WARNING: CONTENTS NOT SUITABLE
FOR HUMAN USE - DO NOT ADMINISTER**

Manufactured for:
 Novartis Pharmaceuticals Corporation
 East Hanover, NJ 07936 85058901

EXP. _____

LOT _____




Suspension

DEMONSTRATION ONLY

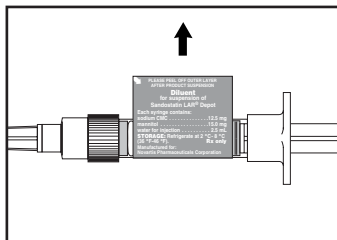
**WARNING: CONTENTS NOT SUITABLE
FOR HUMAN USE - DO NOT ADMINISTER**

Novartis Pharmaceuticals Corporation
 East Hanover, NJ 07936



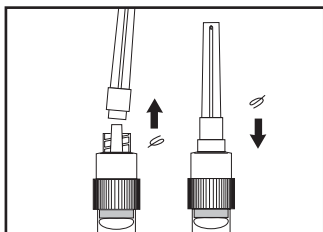
©Novartis
85058901

Step 7



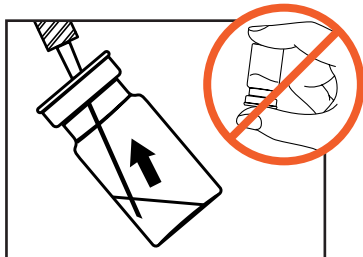
- Peel off outer syringe label

Step 9



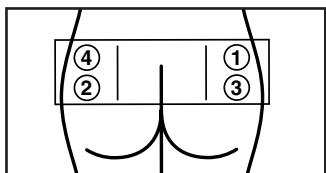
- Draw a small amount of air into the syringe to allow the suspended product to move more freely
- Rock the syringe gently and constantly to maintain a uniform suspension
- Eliminate air from syringe
- **Change the needle**, discarding the first needle and attaching the second supplied needle

Step 8



- Immediately fill the syringe with air, insert the needle through the rubber stopper, and slowly inject all of the air into the vial
- With the bevel down and the vial tipped at approximately a 45-degree angle (as shown in the diagram), slowly draw the entire contents into the syringe **without inverting vial**
- **Some residual suspension will remain** – vial contains overfill

Step 10



- Prepare the injection site with the supplied alcohol wipe
- Rock the syringe gently and constantly to maintain a uniform suspension
- Insert needle deep into right or left gluteus and draw back to ensure that no blood vessel has been penetrated. (If a blood vessel has been penetrated, attach a new 1 1/2" 19 gauge needle and select another injection site)
- Immediately inject contents of entire syringe IM
- **If needle clogs, replace with a new 1 1/2" 19 gauge needle**
- Note: Record injection site on patient's record and **alternate monthly**



1027576

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East Hanover, New Jersey 07936

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REV: 4/04
86000801

Instruction Booklet

Preparation and Administration of



Read this entire booklet before proceeding. If you have questions about preparation and/or administration of Sandostatin LAR® Depot, please call 1-877-LAR-HELP (1-877-527-4357).

ATTENTION:

- Follow enclosed instruction booklet precisely
- Administer immediately after suspension
- Use only 1 1/2" 19 gauge needles
- If needle clogs, replace with a new 1 1/2" 19 gauge needle

Incorrect preparation and/or administration could result in failure of drug delivery.

WARNING: Rubber stopper on vial contains LATEX.

Instructions for Intramuscular (IM) Injection of Sandostatin LAR® Depot (octreotide acetate for injectable suspension)

Important Information for Healthcare Professionals

Successful preparation and administration of Sandostatin LAR® Depot relies on proper suspension technique.

Follow each of the steps outlined in this instruction booklet to ensure complete saturation of the powder and its uniform suspension prior to deep intragluteal injection.

It is recommended that Sandostatin LAR® Depot and the diluent be allowed to **reach room temperature** and then be mixed **immediately** prior to injection. Ensure that the powder is completely suspended at the time of injection.

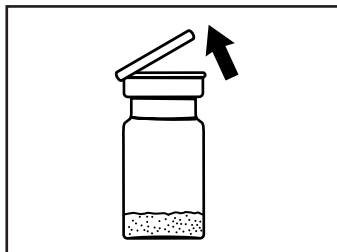
If you have questions about preparation and/or administration of Sandostatin LAR® Depot, please call 1-877-LAR-HELP (1-877-527-4357).

For more information on Sandostatin LAR® Depot, see the enclosed full prescribing information.

Package Contents

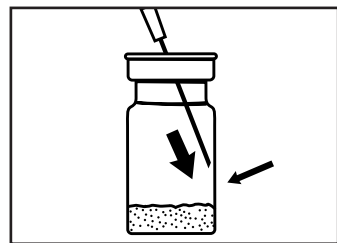
- Vial containing Sandostatin LAR® Depot
- Syringe containing diluent
- Two 1½" 19 gauge needles
- Two alcohol wipes

Step 1



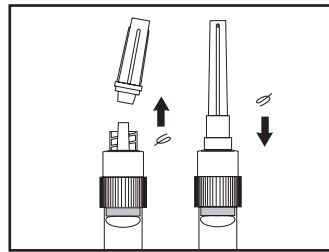
- Allow the vial containing Sandostatin LAR® Depot and the diluent syringe to **reach room temperature** (approximately 30 to 60 minutes)
- Remove the plastic cap from the vial

Step 4



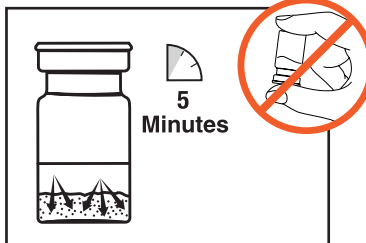
- Insert the needle through the center of the rubber stopper of the Sandostatin LAR® Depot vial
- Without disturbing the Sandostatin LAR® Depot powder, **gently inject contents of syringe down the inside wall of the vial**
- Remove syringe from vial
- Retain the syringe for further use in Step 7

Step 2



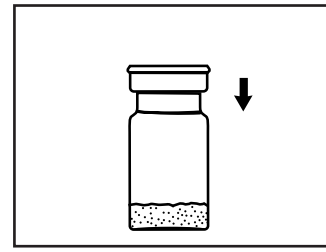
- Remove the cap from the diluent syringe
- Attach one of the supplied needles to the syringe
- Use only 1½" **19 gauge** needles
- **Do not directly inject diluent without preparing suspension**

Step 5



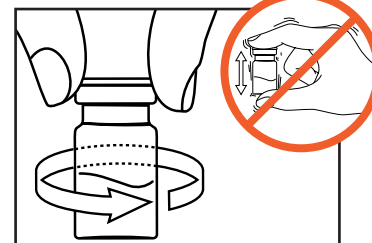
- Do not disturb the vial while diluent saturates the Sandostatin LAR® Depot powder (approximately 5 minutes)
- After 5 minutes, **without** inverting vial, check sides and bottom of vial for dry spots
- **Powder must be completely saturated before proceeding**
- If dry spots exist, allow wetting to continue and check vial every 30 seconds until saturation is complete

Step 3










- **Gently tap** the Sandostatin LAR® Depot vial to ensure that all powder has settled to the bottom
- Clean the Sandostatin LAR® Depot vial stopper with supplied alcohol wipe

Step 6

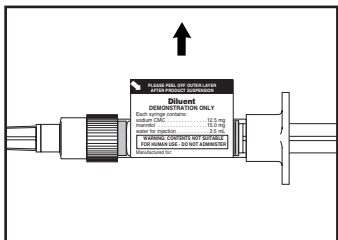


- Once complete saturation has occurred, swirl the vial moderately for 30 to 60 seconds or **until a uniform suspension is achieved**
- **Do not shake or invert the vial**
- The suspension will be milky

SAP-number: 1027576/ 0 replaces in time: -
print date: 23-10-2003
die cut/dimensions: 127 x 76
pharma code: 107
used colours: black (100% 45%), PMS 320 (100%, 70%,40%, 10%)
PMS 179
file name: 1027576.SAN.INSTR.BK.US
made by: Dianne Ligthart

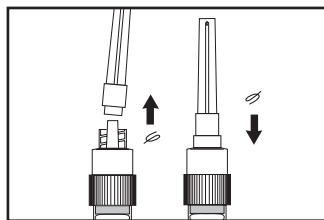
-  Black
-  Black (45% on label)
-  PMS 320 (100% in logo)
-  PMS 320 (70% in logo)
-  PMS 320 (40% in logo)
-  PMS 320 (10% in logo)
-  PMS 179

Step 7



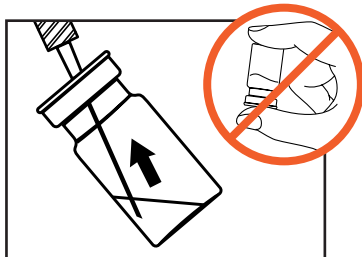
- Peel off outer syringe label

Step 9



- Draw a small amount of air into the syringe to allow the suspended product to move more freely
- Rock the syringe gently and constantly to maintain a uniform suspension
- Eliminate air from syringe
- **Change the needle**, discarding the first needle and attaching the second supplied needle

Step 8



- Immediately fill the syringe with air, insert the needle through the rubber stopper, and slowly inject all of the air into the vial
- With the bevel down and the vial tipped at approximately a 45-degree angle (as shown in the diagram), slowly draw the entire contents into the syringe **without inverting vial**
- **Some residual suspension will remain** – vial contains overfill

YOU HAVE NOW COMPLETED THE TRAINING FOR PREPARATION OF THE SANDOSTATIN LAR® DEPOT USING THE DILUENT SYRINGE.

WARNING:
THE CONTENTS OF THE DEMONSTRATION KIT ARE NOT SUITABLE FOR HUMAN USE.

SYRINGE CONTENTS AND NEEDLES SUPPLIED IN THE DEMONSTRATION KIT SHOULD BE DISCARDED IN A SAFE MANNER.



1027577

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REV: 4/04
86000901

Instruction Booklet

INSTRUCTIONS FOR PROPER SUSPENSION TECHNIQUE

Read this entire booklet before proceeding.
If you have questions about preparation please call 1-877-LAR-HELP (1-877-527-4357).

ATTENTION:

- Contents not suitable for human use
- This kit is for preparation training only
- Use only 1½" 19 gauge needles
- Do not administer the contents of this kit

WARNING: Rubber stopper on vial contains LATEX.

This instruction booklet is being provided as part of a demonstration kit to educate healthcare providers on the proper technique to be employed when reconstituting Sandostatin LAR® Depot (octreotide acetate for injectable suspension) with the diluent syringe.

Important Information for Healthcare Professionals

Successful preparation of Sandostatin LAR® Depot relies on proper suspension technique.

Follow each of the steps outlined in this instruction booklet to ensure complete saturation of the powder and its uniform suspension.

It is recommended that Sandostatin LAR® Depot and the diluent be allowed to **reach room temperature** and then be mixed to ensure that the powder is completely suspended.

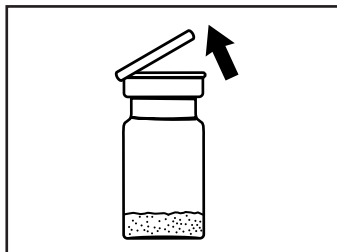
If you have questions about preparation of Sandostatin LAR® Depot, please call 1-877-LAR-HELP (1-877-527-4357).

For more information on Sandostatin LAR® Depot, see the enclosed full prescribing information.

Package Contents

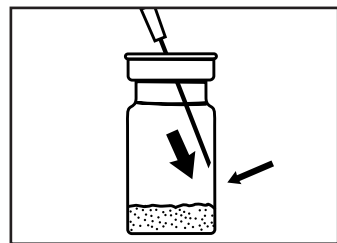
- Vial containing Sandostatin LAR® Depot
- Syringe containing diluent
- Two 1½" 19 gauge needles
- Two alcohol wipes

Step 1



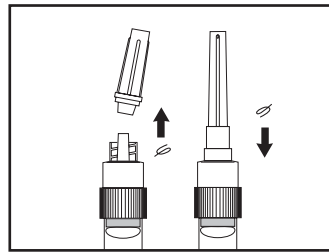
- Allow the vial containing Sandostatin LAR® Depot and the diluent syringe to **reach room temperature** (approximately 30 to 60 minutes)
- Remove the plastic cap from the vial

Step 4



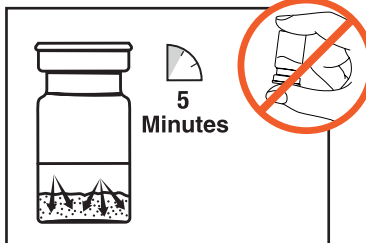
- Insert the needle through the center of the rubber stopper of the Sandostatin LAR® Depot vial
- Without disturbing the Sandostatin LAR® Depot powder, **gently inject contents of syringe down the inside wall of the vial**
- Remove syringe from vial
- Retain the syringe for further use in Step 7

Step 2



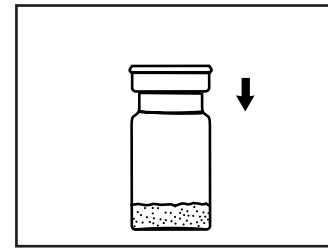
- Remove the cap from the diluent syringe
- Attach one of the supplied needles to the syringe
- Use only 1½" **19 gauge** needles

Step 5



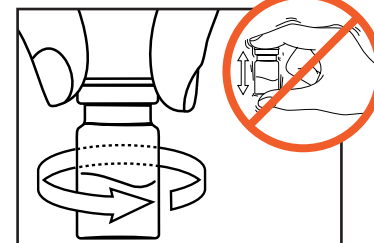
- Do not disturb the vial while diluent saturates the Sandostatin LAR® Depot powder (approximately 5 minutes)
- After 5 minutes, **without** inverting vial, check sides and bottom of vial for dry spots
- **Powder must be completely saturated before proceeding**
- If dry spots exist, allow wetting to continue and check vial every 30 seconds until saturation is complete

Step 3



- **Gently tap** the Sandostatin LAR® Depot vial to ensure that all powder has settled to the bottom
- Clean the Sandostatin LAR® Depot vial stopper with supplied alcohol wipe

Step 6



- Once complete saturation has occurred, swirl the vial moderately for 30 to 60 seconds or **until a uniform suspension is achieved**
- **Do not shake or invert the vial**
- The suspension will be milky

SAP-number: 1027577/ 0 replaces in time: -
print date: 23-10-2003
die cut/dimension: 127 x 76
pharma code: 112
used colours: black, PMS 320, PMS 179
file name: 1027577.SAN.DEMO.BK.US
made by: Dianne Ligthart

 Black
 PMS 320
 PMS 179

- PMS 179
 - PMS 320 (100% in logo)
 - PMS 320 (10% in logo)
 - PMS 320 (40% in logo)
 - PMS 320 (70% in logo)
 - PMS 072 (100%)
 - PMS 072 (40%)
 - Black
- Do not print dotted lines
(FPO) For Position Only


Peel back here

- Contents:**
- Vial containing Sandostatin LAR® Depot
 - Syringe containing diluent
 - Two 1 1/2" 19 gauge needles
 - Two alcohol wipes

10mg
For Intragluteal Injection
NDC 0078-0340-61

WARNING: Rubber stopper on vial contains LATEX.

- ATTENTION:**
- Follow enclosed instruction booklet precisely
 - Use only 1 1/2" 19 gauge needles
 - Administer immediately after suspension
 - If needle clogs, replace with a new 1 1/2" 19 gauge needle
- Incorrect preparation and/or administration could result in failure of drug delivery.

 **Sandostatin LAR® Depot**
(octreotide acetate for injectable suspension)









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Rx only

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-  PMS 320 (100% in logo)
-  PMS 320 (10% in logo)
-  PMS 320 (40% in logo)
-  PMS 320 (70% in logo)
-  PMS 072 (100%)
-  PMS 1375 (100%)
-  PMS 1375 (60%)
-  Black
- Do not print dotted lines
(FPO) For Position Only


Peel back here

- Contents:
- Vial containing Sandostatin LAR[®] Depot
 - Syringe containing diluent
 - Two 1 1/2" 19 gauge needles
 - Two alcohol wipes

20mg

For Intragluteal Injection
NDC 0078-0341-61

WARNING: Rubber stopper on vial contains LATEX.

- ATTENTION:**
- Follow enclosed instruction booklet precisely
 - Use only 1 1/2" 19 gauge needles
 - Administer immediately after suspension
 - If needle clogs, replace with a new 1 1/2" 19 gauge needle
- Incorrect preparation and/or administration could result in failure of drug delivery.









 **Sandostatin LAR[®] Depot**
(octreotide acetate for injectable suspension)

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85059201

-  PMS 320 (100% in logo)
-  PMS 320 (10% in logo)
-  PMS 320 (40% in logo)
-  PMS 320 (70% in logo)
-  PMS 072 (100%)
-  PMS 222 (100%)
-  PMS 222 (40%)
-  Black
- Do not print dotted lines
(FPO) For Position Only


Peel back here

- Contents:**
- Vial containing Sandostatin LAR[®] Depot
 - Syringe containing diluent
 - Two 1 1/2" 19 gauge needles
 - Two alcohol wipes

30mg

For Intragluteal Injection
NDC 0078-0342-61

WARNING: Rubber stopper on vial contains LATEX.

- ATTENTION:**
- Follow enclosed instruction booklet precisely
 - Use only 1 1/2" 19 gauge needles
 - Administer immediately after suspension
 - If needle clogs, replace with a new 1 1/2" 19 gauge needle
- Incorrect preparation and/or administration could result in failure of drug delivery.

 **Sandostatin LAR[®] Depot**
(octreotide acetate for injectable suspension)

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Rx only

30

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- Black
- PMS 032 (100%)
- PMS 032 (20%)
- Do not print dotted lines (FPO) For Position Only

Peel back here 

- Contents:
- Vial containing Sandostatin LAR[®] Depot
 - Syringe containing diluent
 - Two 1 1/2" 19 gauge needles
 - Two alcohol wipes

DEMONSTRATION ONLY

- CONTENTS NOT SUITABLE FOR HUMAN USE
- THIS KIT IS FOR PREPARATION TRAINING ONLY

ATTENTION:

- USE ONLY 1 1/2" 19 GAUGE NEEDLES
- DO NOT ADMINISTER THE CONTENTS OF THIS KIT

DEMONSTRATION ONLY

0078-9342-61

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