NOVARTIS

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-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-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:

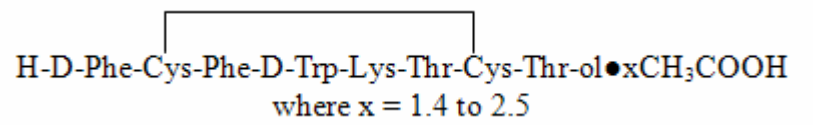
Name of Ingredient	10 mg	20 mg	30 mg
octreotide acetate	11.2 mg*	22.4 mg*	33.6 mg*
D, L-lactic and glycolic acids copolymer	188.8 mg	377.6 mg	566.4 mg
mannitol	41.0 mg	81.9 mg	122.9 mg

*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, $C_{49}H_{66}N_{10}O_{10}S_2$) 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% to 68%, compared to the 163% to 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.

In pediatric patients with hypothalamic obesity, the mean octreotide concentration after 6 doses of 40 mg Sandostatin LAR® Depot administered by IM injection every four weeks was approximately 3.0 ng/mL. Steady-state concentration was achieved after 3 injections of 40 mg dose.

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.

Table 1
Hormonal Response in Acromegalic Patients Receiving 27 to 28 Injections During[1] Treatment with Sandostatin LAR® Depot

	Sandostatin® Injection S.C		Sandostatin LAR® Depot	
Mean Hormone Level	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.

Table 2
Hormonal Response in Acromegalic Patients Receiving 12 Injections During[1] Treatment with Sandostatin LAR® Depot

	Sandostatin® Injection S.C		Sandostatin LAR® Depot	
Mean Hormone Level	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% to 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.

Table 3
Average No. of Daily Stools and Flushing Episodes
in Patients with Malignant Carcinoid Syndrome

		Daily Stools (Average No.)		Daily Flushing Episodes (Average No.)	
Treatment	N	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 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 T_4) is recommended during chronic octreotide therapy (see ADVERSE REACTIONS).

Cardiac Function

In both 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 B_{12} levels and abnormal Schilling's tests have been observed in some patients receiving octreotide therapy, and monitoring of vitamin B_{12} 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 T_4 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., quinidine, terfenadine) should therefore be used with caution.

Drug Laboratory Test Interactions

No known interference exists with clinical laboratory tests, including amine or peptide determinations.

Carcinogenesis/Mutagenesis/Impairment of Fertility

Studies in laboratory animals have demonstrated no mutagenic potential of Sandostatin®. No mutagenic potential of the polymeric carrier in Sandostatin LAR® Depot, D,L-lactic and glycolic acids copolymer, was observed in the Ames mutagenicity test.

No carcinogenic potential was demonstrated in mice treated subcutaneously with octreotide for 85-99 weeks at doses up to 2000 mcg/kg/day (8x the human exposure based on body surface area). In a 116-week subcutaneous study in rats administered octreotide, a 27% and 12% incidence of injection site sarcomas or squamous cell carcinomas was observed in males and females, respectively, at the highest dose level of 1250 mcg/kg/day (10x the human exposure based on body surface area) compared to an incidence of 8%-10% in the vehicle-control groups. The increased incidence of injection site tumors was most probably caused by irritation and the high sensitivity of the rat to repeated subcutaneous injections at the same site. Rotating injection sites would prevent chronic irritation in humans. There have been no reports of injection site tumors in patients treated with Sandostatin® Injection for at least 5 years. There was also a 15% incidence of uterine adenocarcinomas in the 1250 mcg/kg/day females compared to 7% in the saline-control females and 0% in the vehicle-control females. The presence of endometritis coupled with the absence of corpora lutea, the reduction in mammary fibroadenomas, and the presence of uterine dilatation suggest that the uterine tumors were associated with estrogen dominance in the aged female rats which does not occur in humans.

Octreotide did not impair fertility in rats at doses up to 1000 mcg/kg/day, which represents 7x the human exposure based on body surface area.

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to 16 times the highest human dose based on body surface area and have revealed no evidence of impaired

fertility or harm to the fetus due to octreotide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in milk, caution should be exercised when Sandostatin LAR® Depot is administered to a nursing woman.

Pediatric Use

The efficacy and safety of Sandostatin LAR Depot were examined in a randomized, double-blind, placebo-controlled six-month study in 60 pediatric patients aged 6 – 17 years with hypothalamic obesity resulting from cranial insult. Mean BMI increased 0.1 kg/m^2 in Sandostatin LAR Depot–treated subjects compared to 0.0 kg/m^2 in saline control-treated subjects. Diarrhea occurred in 11 of 30 (37%) patients treated with Sandostatin LAR Depot. No unexpected adverse events were observed. However, with Sandostatin LAR Depot 40 mg once a month, the incidence of new cholelithiasis in this pediatric population (33%) was higher than that seen in other adult indications such as acromegaly (22%) or malignant carcinoid syndrome (24%), where Sandostatin LAR Depot dosing was 10 to 30 mg once a month.

Experience with Sandostatin Injection in the pediatric population is limited. Its use has been primarily in patients with congenital hyperinsulinism (also called nesidioblastosis). The youngest patient to receive the drug was 1 month old. At doses of 1-40 mcg/kg body weight/day, the majority of side effects observed were gastrointestinal- steatorrhea, diarrhea, vomiting and abdominal distention. Poor growth has been reported in several patients treated with Sandostatin® Injection for more than 1 year; catch-up growth occurred after Sandostatin® Injection was discontinued. A 16-month-old male with enterocutaneous fistula developed sudden abdominal pain and increased nasogastric drainage and died 8 hours after receiving a single 100 mcg subcutaneous dose of Sandostatin® Injection.

Geriatric Use

Clinical studies of Sandostatin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS (See WARNINGS and PRECAUTIONS)

Gallbladder abnormalities, especially stones and/or biliary sludge, frequently develop in patients on chronic octreotide therapy (see WARNINGS). Few patients, however, develop acute symptoms requiring cholecystectomy.

Cardiac

In acromegalics, sinus bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias developed in 9% of patients during Sandostatin® (octreotide acetate) Injection therapy. Electrocardiograms were performed only in carcinoid patients receiving Sandostatin LAR® Depot (octreotide acetate for injectable suspension). In carcinoid syndrome patients sinus bradycardia developed in 19%; conduction abnormalities occurred in 9%, and arrhythmias developed in 3%. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease (see PRECAUTIONS).

Gastrointestinal

The most common symptoms are gastrointestinal. The overall incidence of the most frequent of these symptoms in clinical trials of acromegalic patients treated for approximately 1 to 4 years is shown in Table 4.

Table 4
Number (%) of Acromegalic Patients with Common G.I. Adverse Events

	Sandostatin® Injection S.C t.i.d n=114		Sandostatin LAR® Depot q. 28 days n=261	
Adverse Event	N	%	N	%
Diarrhea	66	(57.9)	95	(36.4)
Abdominal Pain or Discomfort	50	(43.9)	76	(29.1)
Flatulence	15	(13.2)	67	(25.7)
Constipation	10	(8.8)	49	(18.8)
Nausea	34	(29.8)	27	(10.3)
Vomiting	5	(4.4)	17	(6.5)

Only 2.6% of the patients on Sandostatin® Injection in U.S. clinical trials discontinued therapy due to these symptoms. No acromegalic patient receiving Sandostatin LAR® Depot discontinued therapy for a G.I. event.

In patients receiving Sandostatin LAR® Depot the incidence of diarrhea was dose related. Diarrhea, abdominal pain, and nausea developed primarily during the first month of treatment with Sandostatin LAR® Depot. Thereafter, new cases of these events were uncommon. The vast majority of these events were mild-to-moderate in severity.

In rare instances gastrointestinal adverse effects may resemble acute intestinal obstruction, with progressive abdominal distention, severe epigastric pain, abdominal tenderness, and guarding.

Dyspepsia, steatorrhea, discoloration of feces, and tenesmus were reported in 4%-6% of patients.

In a clinical trial of carcinoid syndrome, nausea, abdominal pain, and flatulence were reported in 27%-38% and constipation or vomiting in 15%-21% of patients treated with Sandostatin LAR® Depot. Diarrhea was reported as an adverse event in 14% of patients but since most of the patients had diarrhea as a symptom of carcinoid syndrome, it is difficult to assess the actual incidence of drug-related diarrhea.

Hypo/Hyperglycemia

In acromegaly patients treated with either Sandostatin® Injection or Sandostatin LAR® Depot, hypoglycemia occurred in approximately 2% and hyperglycemia in approximately 15% of patients. In carcinoid patients, hypoglycemia occurred in 4% and hyperglycemia in 27% of patients treated with Sandostatin LAR® Depot (see PRECAUTIONS).

Hypothyroidism

In acromegaly patients receiving Sandostatin® Injection, 12% developed biochemical hypothyroidism, 8% developed goiter, and 4% required initiation of thyroid replacement therapy while receiving Sandostatin® Injection. In acromegalics treated with Sandostatin LAR® Depot hypothyroidism was reported as an adverse event in 2% and goiter in 2%. Two patients receiving Sandostatin LAR® Depot, required initiation of thyroid hormone replacement therapy. In carcinoid patients, hypothyroidism has only been reported in isolated patients and goiter has not been reported (see PRECAUTIONS).

Pain At the Injection Site

Pain on injection, which is generally mild-to-moderate, and short-lived (usually about 1 hour) is dose-related, being reported by 2%, 9%, and 11% of acromegalics receiving doses of 10 mg, 20 mg and 30 mg, respectively, of Sandostatin LAR® Depot. In carcinoid patients, where a diary was kept, pain at the injection site was reported by about 20%-25% at a 10-mg dose and about 30%-50% at the 20-mg and 30-mg dose.

Other Adverse Events 16%-20%

Other adverse events (relationship to drug not established) in acromegalic and/or carcinoid syndrome patients receiving Sandostatin LAR® Depot were upper respiratory infection, flu-like symptoms, fatigue, dizziness, headache, malaise, fever, dyspnea, back pain, chest pain, arthropathy.

Other Adverse Events 5%-15%

Other adverse events (relationship to drug not established) occurring in an incidence of 5%-15% in patients receiving Sandostatin LAR® Depot were:
Body As a Whole: asthenia, rigors, allergy
Cardiovascular: hypertension, peripheral edema
Central and Peripheral Nervous System: paresthesia, hypoesthesia
Gastrointestinal: dyspepsia, anorexia, hemorrhoids
Hearing and Vestibular: earache
Heart Rate and Rhythm: palpitations
Hematologic: anemia
Metabolic and Nutritional: dehydration, weight decrease

Musculoskeletal System: myalgia, leg cramps, arthralgia
Psychiatric: depression, anxiety, confusion, insomnia
Resistance Mechanism: viral infection, otitis media
Respiratory System: coughing, pharyngitis, rhinitis, sinusitis
Skin and Appendages: rash, pruritus, increased sweating
Urinary System: urinary tract infection, renal calculus

Other Adverse Events 1%-4%

Other events (relationship to drug not established), each occurring in an incidence of 1%-4% in patients receiving Sandostatin LAR® Depot and reported by at least 2 patients were:
Application Site: injection site inflammation
Body As a Whole: syncope, ascites, hot flushes
Cardiovascular: cardiac failure, angina pectoris, hypertension aggravated
Central and Peripheral Nervous System: vertigo, abnormal gait, neuropathy, neuralgia, tremor, dysphonia, hyperkinesia, hypertonia
Gastrointestinal: rectal bleeding, melena, gastritis, gastroenteritis, colitis, gingivitis, taste perversion, stomatitis, glossitis, dry mouth, dysphagia, steatorrhea, diverticulitis
Hearing and Vestibular: tinnitus
Heart Rate and Rhythm: tachycardia
Liver and Biliary: jaundice
Metabolic and Nutritional: hypokalemia, cachexia, gout, hypoproteinemia
Platelet, Bleeding, Clotting: pulmonary embolism, epistaxis
Psychiatric: amnesia, somnolence, nervousness, hallucinations
Reproductive, Female: menstrual irregularities, breast pain
Reproductive, Male: impotence
Resistance Mechanism: cellulitis, renal abcess, moniliasis, bacterial infection
Respiratory System: bronchitis, pneumonia, pleural effusion
Skin and Appendages: alopecia, urticaria, acne
Urinary System: incontinence, albuminuria
Vascular: cerebral vascular disorder, phlebitis, hematoma
Vision: abnormal vision

Rare Adverse Events

Other events (relationship to drug not established) of potential clinical significance occurring rarely (<1%) in clinical trials of octreotide either as Sandostatin® Injection or Sandostatin LAR® Depot, or reported post-marketing in patients with acromegaly, carcinoid syndrome, or other disorders include:
Body As a Whole: anaphylactoid reactions, including anaphylactic shock, facial edema, generalized edema, abdomen enlarged, malignant hyperpyrexia
Cardiovascular: aneurysm, myocardial infarction, angina pectoris, aggravated, pulmonary hypertension, cardiac arrest, orthostatic hypotension
Central and Peripheral Nervous System: hemiparesis, paresis, convulsions, paranoia, pituitary apoplexy, visual field defect, migraine, aphasia, scotoma, Bell's palsy
Endocrine Disorders: hypoadrenalism, diabetes insipidus, gynecomastia, galactorrhea

Gastrointestinal: G.I. hemorrhage, intestinal obstruction, hepatitis, increase in liver enzymes, fatty liver, peptic/gastric ulcer, gallbladder polyp, appendicitis, pancreatitis
Hearing and Vestibular: deafness
Heart Rate and Rhythm: atrial fibrillation
Hematologic: pancytopenia, thrombocytopenia
Metabolic and Nutritional: renal insufficiency, creatinine increased, CK increased, diabetes mellitus
Musculoskeletal: Raynaud's syndrome, arthritis, joint effusion
Neoplasms: breast carcinoma, basal cell carcinoma
Platelet, Bleeding, and Clotting: arterial thrombosis of the arm
Psychiatric: suicide attempt, libido decrease
Reproductive, Female: lactation, nonpuerperal
Respiratory: pulmonary nodule, status asthmaticus, pneumothorax
Skin and Appendages: cellulitis, petechiae, urticaria
Urinary System: renal failure, hematuria
Vascular: intracranial hemorrhage, retinal vein thrombosis
Vision: glaucoma

Antibodies to Octreotide

Studies to date have shown that antibodies to octreotide develop in up to 25% of patients treated with octreotide acetate. These antibodies do not influence the degree of efficacy response to octreotide; however, in two acromegalic patients who received Sandostatin® Injection, the duration of GH suppression following each injection was about twice as long as in patients without antibodies. It has not been determined whether octreotide antibodies will also prolong the duration of GH suppression in patients being treated with Sandostatin LAR® Depot.

OVERDOSAGE

No frank overdose has occurred in any patient to date. Sandostatin® (octreotide acetate) Injection given in intravenous bolus doses of 1 mg (1000 mcg) to healthy volunteers did not result in serious ill effects, nor did doses of 30 mg (30,000 mcg) given IV over 20 minutes and of 120 mg (120,000 mcg) given IV over 8 hours to research patients. Doses of 2.5 mg (2500 mcg) of Sandostatin® Injection subcutaneously have, however, caused hypoglycemia, flushing, dizziness, and nausea.

Up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Regional Poison Control Centers are listed in the Physicians' Desk Reference®*.

Mortality occurred in mice and rats given 72 mg/kg and 18 mg/kg IV, respectively, of octreotide.

Drug Abuse and Dependence

There is no indication that octreotide has potential for drug abuse or dependence. Octreotide levels in the central nervous system are negligible, even after doses up to 30,000 mcg.

DOSAGE AND ADMINISTRATION

Sandostatin LAR® Depot (octreotide acetate for injectable suspension) must be administered under the supervision of a physician. **Do not directly inject diluent without preparing suspension.** It is important to closely follow the mixing instructions included in the packaging. Sandostatin LAR® Depot must be administered immediately after mixing. Sandostatin LAR® Depot should be administered intragluteally at four-week intervals. Administration of Sandostatin LAR® Depot at intervals greater than 4 weeks is not recommended because there is no adequate information on whether such patients could be satisfactorily controlled. Deltoid injections are to be avoided because of significant discomfort at the injection site when given in that area. **Sandostatin LAR® Depot should never be administered by the IV or S.C. routes.** The following dosage regimens are recommended.

Acromegaly

1. Patients Not Currently Receiving Octreotide Acetate

Patients not currently receiving octreotide acetate should begin therapy with Sandostatin® (octreotide acetate) Injection given subcutaneously in an initial dose of 50 mcg t.i.d. Beginning with this low dose may permit adaptation to adverse gastrointestinal effects for patients who require higher doses. Multiple growth hormone (GH) determinations at 0-8 hours after a subcutaneous Sandostatin® Injection will guide dosage titration. The goal is to attempt to normalize GH and IGF-1 (somatomedin C) levels. Most patients require doses of 100 mcg to 200 mcg t.i.d. for maximum effect but some patients require up to 500 mcg t.i.d. Injection sites should be rotated in a systematic manner to avoid irritation.

Although responsiveness of GH to octreotide acetate can be ascertained quickly, patients should be maintained on Sandostatin® Injection s.c. for at least 2 weeks to determine tolerance to octreotide.

The most common adverse events are gastrointestinal, which usually begin within the first few days of administration and usually subside within 2 to 8 weeks. In clinical trials, <3% of patients discontinued Sandostatin® Injection because of G.I. symptoms.

Patients who are considered to be "responders" to the drug, based on GH and IGF-1 levels, and who tolerate the drug, can then be switched to Sandostatin LAR® Depot in the dosage scheme described under 2, below [Patients Currently Receiving Sandostatin® Injection].

2. Patients Currently Receiving Sandostatin® (octreotide acetate) Injection

Patients currently receiving Sandostatin® Injection can be switched directly to Sandostatin LAR® Depot in a dose of 20 mg given IM intragluteally at 4-week intervals for 3 months. **(Deltoid injections are to be avoided because of significant discomfort at the injection site when given in that area.)** Gluteal injection sites should be alternated to avoid irritation.

At the end of 3 months Sandostatin LAR® Depot dosage may be continued at the same level or increased or decreased based on the following regimen:

GH ≤2.5 ng/mL, IGF-1 normal and clinical symptoms controlled: maintain Sandostatin LAR® Depot dosage at 20 mg every 4 weeks.

GH >2.5 ng/mL, IGF-1 elevated, and/or clinical symptoms uncontrolled, increase Sandostatin LAR® Depot dosage to 30 mg every 4 weeks.

GH ≤1 ng/mL, IGF-1 normal and clinical symptoms controlled, reduce Sandostatin LAR® Depot dosage to 10 mg every 4 weeks.

Patients whose GH, IGF-1, and symptoms are not adequately controlled at a dose of 30 mg may have the dose increased to 40 mg every 4 weeks. Doses higher than 40 mg are not recommended.

Administration of Sandostatin LAR® Depot at intervals greater than 4 weeks is not recommended because there is no adequate information on whether such patients could be satisfactorily controlled.

In patients who have received pituitary irradiation, Sandostatin LAR® Depot should be withdrawn yearly for approximately 8 weeks to assess disease activity. If GH or IGF-1 levels increase and signs and symptoms recur, Sandostatin LAR® Depot therapy may be resumed.

3. Special Populations: Renal Failure

In patients with renal failure requiring dialysis, the half-life of octreotide may be increased, necessitating adjustment of the maintenance dosage (see CLINICAL PHARMACOLOGY and Pharmacokinetics of Octreotide Acetate).

Carcinoid Tumors and VIPomas

1. Patients Not Currently Receiving Octreotide Acetate

Patients not currently receiving octreotide acetate should begin therapy with Sandostatin® Injection given subcutaneously. The suggested daily dosage for carcinoid tumors during the first 2 weeks of therapy ranges from 100-600 mcg/day in 2-4 divided doses (mean daily dosage is 300 mcg). Some patients may require doses up to 1500 mcg/day. The suggested daily dosage for VIPomas is 200-300 mcg in 2-4 divided doses (range 150-750 mcg); dosage may be adjusted on an individual basis to control symptoms but usually doses above 450 mcg/day are not required.

Sandostatin® Injection should be continued for at least 2 weeks. Thereafter, patients who are considered "responders" to octreotide acetate and who tolerate the drug may be switched to Sandostatin LAR® Depot in the dosage regimen described under 2, below (Patients Currently Receiving Sandostatin® Injection).

2. Patients Currently Receiving Sandostatin® (octreotide acetate) Injection

Patients currently receiving Sandostatin® Injection can be switched to Sandostatin LAR® Depot in a dosage of 20 mg given IM intragluteally at 4-week intervals for 2 months. **Deltoid injections are to be avoided because of significant discomfort at the injection site when given in that area**. Gluteal injection sites should be alternated to avoid irritation. Because of the need for serum octreotide to reach therapeutically effective levels following initial injection of Sandostatin LAR® Depot, carcinoid tumor and VIPoma patients should continue to receive Sandostatin® Injection s.c. for at least 2 weeks in the same dosage they were taking before the switch. Failure to continue subcutaneous injections for this period may result in exacerbation of symptoms. (Some patients may require 3 or 4 weeks of such therapy.)

After two months of a 20-mg dosage of Sandostatin LAR® Depot, dosage may be increased to 30 mg every 4 weeks if symptoms are not adequately controlled. Patients who achieve good control on a 20-mg dose may have their dose lowered to 10-mg for a trial

period. If symptoms recur, dosage should then be increased to 20 mg every 4 weeks. Many patients can, however, be satisfactorily maintained at a 10 mg dosage every 4 weeks. A dose of 10 mg is not recommended as a starting dose, however, because therapeutically effective levels of octreotide are reached more rapidly with a 20-mg dose.

Dosages higher than 30 mg are not recommended because there is no information on their usefulness.

Despite good overall control of symptoms, patients with carcinoid tumors and VIPomas often experience periodic exacerbation of symptoms (regardless of whether they are being maintained on Sandostatin® Injection or Sandostatin LAR® Depot). During these periods they may be given Sandostatin® Injection s.c. for a few days at the dosage they were receiving prior to switch to Sandostatin LAR® Depot. When symptoms are again controlled, the Sandostatin® Injection s.c. can be discontinued.

Administration of Sandostatin LAR® Depot at intervals greater than 4 weeks is not recommended because there is no adequate information on whether such patients could be adequately controlled.

3. Special Populations: Renal Failure

In patients with renal failure requiring dialysis, the half-life of octreotide may be increased, necessitating adjustment of the maintenance dosage (see CLINICAL PHARMACOLOGY and Pharmacokinetics of Octreotide Acetate).

HOW SUPPLIED

Sandostatin LAR® Depot (octreotide acetate for injectable suspension) is available in single-use kits containing a 5 mL vial of 10 mg, 20 mg or 30 mg strength, a syringe containing 2.5 mL of diluent, two sterile 1½" 19 gauge needles, and two alcohol wipes. An instruction booklet for the preparation of drug suspension for injection is also included with each kit.

Drug Product Kits

10 mg kit……...NDC 0078-0340-61
20 mg kit……...NDC 0078-0341-61
30 mg kit……...NDC 0078-0342-61
Demonstration kit…….NDC 0078-9342-61

Storage

For prolonged storage, Sandostatin LAR® Depot should be stored at refrigerated temperatures between 2°C and 8°C (36°F-46°F) and protected from light until the time of use. Sandostatin LAR® Depot drug product kit should remain at room temperature for 30-60 minutes prior to preparation of the drug suspension. However, after preparation the drug suspension must be administered immediately.

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NOVARTIS

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