Sandostatin®
octreotide acetate

Injection

Rx Only

Prescribing Information

DESCRIPTION

Sandostatin® (octreotide acetate) Injection, a cyclic octapeptide prepared as a clear sterile solution of octreotide, acetate salt, in a buffered lactic acid solution for administration by deep subcutaneous (intrafat) or intravenous injection. Octreotide acetate, known chemically as L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2→7)-disulfide; [R-(R*, R*)] acetate salt, is a long-acting octapeptide with pharmacologic actions mimicking those of the natural hormone somatostatin.

Sandostatin Injection is available as: sterile 1-mL ampuls in 3 strengths, containing 50, 100, or 500 mcg octreotide (as acetate), and sterile 5-mL multi-dose vials in 2 strengths, containing 200 and 1000 mcg/mL of octreotide (as acetate).

Each ampul also contains:

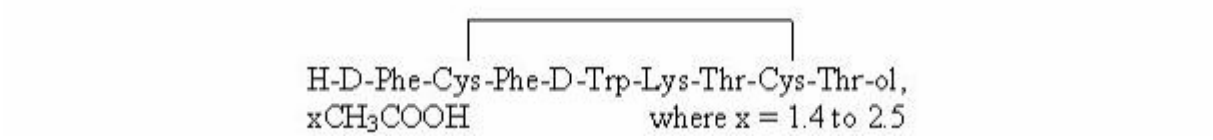
lactic acid, USP	3.4 mg
mannitol, USP	45 mg
sodium bicarbonate, USP	qs to pH 4.2 ± 0.3
water for injection, USP	qs to 1 mL

Each mL of the multi-dose vials also contains:

lactic acid, USP	3.4 mg
mannitol, USP	45 mg
phenol, USP	5.0 mg
sodium bicarbonate, USP	qs to pH 4.2 ± 0.3
water for injection, USP	qs to 1 mL

Lactic acid and sodium bicarbonate are added to provide a buffered solution, pH to 4.2 ± 0.3.

The molecular weight of octreotide acetate is 1019.3 (free peptide, $C_{49}H_{66}N_{10}O_{10}S_2$) and its amino acid sequence is:



CLINICAL PHARMACOLOGY

Sandostatin® (octreotide acetate) 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, Sandostatin has been used to treat the symptoms associated with metastatic carcinoid tumors (flushing and diarrhea), and Vasoactive Intestinal Peptide (VIP) secreting adenomas (watery diarrhea).

Sandostatin substantially reduces growth hormone and/or IGF-I (somatomedin C) levels in patients with acromegaly.

Single doses of Sandostatin 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*).

Sandostatin suppresses secretion of thyroid stimulating hormone (TSH).

Pharmacokinetics

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 after intravenous single doses up to 200 mcg and subcutaneous single doses up to 500 mcg and after subcutaneous multiple doses up to 500 mcg t.i.d. (1500 mcg/day).

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 ranged from 7 L/hr to 10 L/hr. In blood, the distribution 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 to 1.9 hours compared with 1-3 minutes with the natural hormone. The duration of action of Sandostatin is variable but extends up to 12 hours depending upon the type of tumor. 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 renal impairment the elimination of octreotide from plasma was prolonged and total body clearance reduced. In mild renal impairment (Cl_{CR} 40-60 mL/min) octreotide $t_{1/2}$ was 2.4 hours and total body clearance was 8.8 L/hr, in moderate impairment (Cl_{CR} 10-39 mL/min) $t_{1/2}$ was 3.0 hours and total body clearance 7.3 L/hr, and in severely renally impaired

patients not requiring dialysis (Cl_{CR} <10 mL/min) $t_{1/2}$ was 3.1 hours and total body clearance was 7.6 L/hr. In patients with severe renal failure requiring dialysis, total body clearance was reduced to about half that found in healthy subjects (from approximately 10 L/hr to 4.5 L/hr).

Patients with liver cirrhosis showed prolonged elimination of drug, with octreotide $t_{1/2}$ increasing to 3.7 hr and total body clearance decreasing to 5.9 L/hr, whereas patients with fatty liver disease showed $t_{1/2}$ increased to 3.4 hr and total body clearance of 8.2 L/hr.

INDICATIONS AND USAGE

Acromegaly

Sandostatin® (octreotide acetate) is indicated to reduce blood levels of growth hormone and IGF-I (somatomedin C) in acromegaly patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptine mesylate at maximally tolerated doses. The goal is to achieve normalization of growth hormone and IGF-I (somatomedin C) levels (*see DOSAGE AND ADMINISTRATION*). In patients with acromegaly, Sandostatin reduces growth hormone to within normal ranges in 50% of patients and reduces IGF-I (somatomedin C) to within normal ranges in 50%-60% of patients. Since the effects of pituitary irradiation may not become maximal for several years, adjunctive therapy with Sandostatin to reduce blood levels of growth hormone and IGF-I (somatomedin C) offers potential benefit before the effects of irradiation are manifested.

Improvement in clinical signs and symptoms or reduction in tumor size or rate of growth were not shown in clinical trials performed with Sandostatin; these trials were not optimally designed to detect such effects.

Carcinoid Tumors

Sandostatin is indicated for the symptomatic treatment of patients with metastatic carcinoid tumors where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease.

Sandostatin studies were not designed to show an effect on the size, rate of growth or development of metastases.

Vasoactive Intestinal Peptide Tumors (VIPomas)

Sandostatin is indicated for the treatment of the profuse watery diarrhea associated with VIP-secreting tumors. Sandostatin studies were not designed to show an effect on the size, rate of growth or development of metastases.

CONTRAINDICATIONS

Sensitivity to this drug or any of its components.

WARNINGS

Single doses of Sandostatin® (octreotide acetate) have been shown to inhibit gallbladder contractility and decrease bile secretion in normal volunteers. In clinical trials (primarily patients with acromegaly or psoriasis), 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 for 12 months or longer was 52%. Less than 2% of patients treated with Sandostatin for 1 month or less developed gallstones. The incidence of gallstones did not appear related to age, sex or dose. Like patients without gallbladder abnormalities, the majority of patients developing gallbladder abnormalities on ultrasound had gastrointestinal symptoms. The symptoms were not specific for gallbladder disease. A few patients developed acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, or pancreatitis during Sandostatin therapy or following its withdrawal. One patient developed ascending cholangitis during Sandostatin therapy and died.

PRECAUTIONS

General

Sandostatin® (octreotide acetate) alters the balance between the counter-regulatory hormones, insulin, glucagon and growth hormone, which may result in hypoglycemia or hyperglycemia. Sandostatin also suppresses secretion of thyroid stimulating hormone, which may result in hypothyroidism. Cardiac conduction abnormalities have also occurred during treatment with Sandostatin. However, the incidence of these adverse events during long-term therapy was determined vigorously only in acromegaly patients who, due to their underlying disease and/or the subsequent treatment they receive, are at an increased risk for the development of diabetes mellitus, hypothyroidism, and cardiovascular disease. Although the degree to which these abnormalities are related to Sandostatin therapy is not clear, new abnormalities of glycemic control, thyroid function and ECG developed during Sandostatin therapy as described below.

Risk of Pregnancy with Normalization of IGF-1 and GH

Although acromegaly may lead to infertility, there are reports of pregnancy in acromegalic women. In women with active acromegaly who have been unable to become pregnant, normalization of GH and IGF-1 may restore fertility. Female patients of childbearing potential should be advised to use adequate contraception during treatment with octreotide.

The hypoglycemia or hyperglycemia which occurs during Sandostatin therapy is usually mild, but may result in overt diabetes mellitus or necessitate dose changes in insulin or other hypoglycemic agents. Hypoglycemia and hyperglycemia occurred on Sandostatin in 3% and 16% of acromegalic patients, respectively. Severe hyperglycemia, subsequent pneumonia, and death following initiation of Sandostatin therapy was reported in one patient with no history of hyperglycemia.

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.

In acromegalic patients, 12% developed biochemical hypothyroidism only, 8% developed goiter, and 4% required initiation of thyroid replacement therapy while receiving Sandostatin. Baseline and periodic assessment of thyroid function (TSH, total and/or free T_4) is recommended during chronic therapy.

In acromegalics, bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias occurred in 9% of patients during Sandostatin therapy. Other EKG changes observed included QT prolongation, axis shifts, early repolarization, low voltage, R/S transition, and early R wave progression. These ECG changes are not uncommon in acromegalic patients. 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 therapy resulted in worsening of CHF with improvement when drug was discontinued. Confirmation of a drug effect was obtained with a positive rechallenge.

Several cases of pancreatitis have been reported in patients receiving Sandostatin therapy.

Sandostatin may alter absorption of dietary fats in some patients.

In patients with severe renal failure requiring dialysis, the half-life of Sandostatin may be increased, necessitating adjustment of the maintenance dosage.

Depressed vitamin B_{12} levels and abnormal Schilling's tests have been observed in some patients receiving Sandostatin therapy, and monitoring of vitamin B_{12} levels is recommended during chronic Sandostatin therapy.

Information for Patients

Careful instruction in sterile subcutaneous injection technique should be given to the patients and to other persons who may administer Sandostatin Injection.

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-I (somatomedin C) Responsiveness to Sandostatin may be evaluated by determining growth hormone levels at 1-4 hour intervals for 8-12 hours post dose. Alternatively, a single measurement of IGF-I (somatomedin C) level may be made two weeks after drug initiation or dosage change.
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

Sandostatin has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs. Concomitant administration of Sandostatin 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 carcinogenic potential was demonstrated in mice treated subcutaneously 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, 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 for up to 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.

Sandostatin 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

There are no adequate and well-controlled studies of octreotide use in pregnant women. Reproduction studies have been performed in rats and rabbits at doses up to 16 times the highest recommended human dose based on body surface area and revealed no evidence of harm to the fetus due to octreotide. However, because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

In postmarketing data, a limited number of exposed pregnancies have been reported in patients with acromegaly. Most women were exposed to octreotide during the first trimester of pregnancy at doses ranging from 100-300 mcg/day of Sandostatin s.c. or 20-30 mg/month of Sandostatin LAR, however some women elected to continue octreotide therapy throughout pregnancy. In cases with a known outcome, no congenital malformations were reported.

Nursing Mothers

It is not known whether octreotide is excreted into human milk. Because many drugs are excreted in human milk, caution should be exercised when octreotide is administered to a nursing woman.

Pediatric Use

Safety and efficacy of Sandostatin Injection in the pediatric population have not been demonstrated.

No formal controlled clinical trials have been performed to evaluate the safety and effectiveness of Sandostatin in pediatric under age 6 years. In post-marketing report, serious adverse events, including hypoxia, necrotizing enterocolitis, and death, have been reported with Sandostatin use in children, most notably in children under 2 years of age. The relationship of these events to octreotide has not been established as the majority of these pediatric patients had serious underlying co-morbid conditions.

The efficacy and safety of Sandostatin using the Sandostatin LAR Depot formulation was examined in a single randomized, double-blind, placebo-controlled, six–month pharmacokinetics study in 60 pediatric patients age 6-17 years with hypothalamic obesity resulting from cranial insult. The mean octreotide concentration after 6 doses of 40 mg Sandostatin LAR Depot administered by IM injection every four weeks was approximately 3 ng/ml. Steady-state concentrations was achieved after 3 injections of a 40 mg dose. 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. Efficacy was not demonstrated. 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 adults indications such as acromegaly (22%) or malignant carcinoid syndrome (24%), where Sandostatin LAR Depot was 10 to 30 mg once a month.

.

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

Gallbladder Abnormalities

Gallbladder abnormalities, especially stones and/or biliary sludge, frequently develop in patients on chronic Sandostatin® (octreotide acetate) therapy (*see WARNINGS*).

Cardiac

In acromegalics, sinus bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias developed in 9% of patients during Sandostatin therapy (*see PRECAUTIONS – General).*

Gastrointestinal

Diarrhea, loose stools, nausea and abdominal discomfort were each seen in 34%-61% of acromegalic patients in U.S. studies although only 2.6% of the patients discontinued therapy due to these symptoms. These symptoms were seen in 5%-10% of patients with other disorders.

The frequency of these symptoms was not dose-related, but diarrhea and abdominal discomfort generally resolved more quickly in patients treated with 300 mcg/day than in those treated with 750 mcg/day. Vomiting, flatulence, abnormal stools, abdominal distention, and constipation were each seen in less than 10% of patients.

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

Hypo/Hyperglycemia

Hypoglycemia and hyperglycemia occurred in 3% and 16% of acromegalic patients, respectively, but only in about 1.5% of other patients. Symptoms of hypoglycemia were noted in approximately 2% of patients.

Hypothyroidism

In acromegalics, biochemical hypothyroidism alone occurred in 12% while goiter occurred in 6% during Sandostatin therapy (*see PRECAUTIONS – General).* In patients without acromegaly, hypothyroidism has only been reported in several isolated patients and goiter has not been reported.

Other Adverse Events

Pain on injection was reported in 7.7%, headache in 6% and dizziness in 5%. Pancreatitis was also observed (*see WARNINGS and PRECAUTIONS).*

Other Adverse Events 1%-4%

Other events (relationship to drug not established), each observed in 1%-4% of patients, included fatigue, weakness, pruritus, joint pain, backache, urinary tract infection, cold symptoms, flu symptoms, injection site hematoma, bruise, edema, flushing, blurred vision, pollakiuria, fat malabsorption, hair loss, visual disturbance and depression.

Other Adverse Events <1%

Events reported in less than 1% of patients and for which relationship to drug is not established are listed: *Gastrointestinal:* hepatitis, jaundice, increase in liver enzymes, GI bleeding, hemorrhoids, appendicitis, gastric/peptic ulcer, gallbladder polyp; *Integumentary:* rash, cellulitis, petechiae, urticaria, basal cell carcinoma; *Musculoskeletal:* arthritis, joint effusion, muscle pain, Raynaud's phenomenon; *Cardiovascular:* chest pain, shortness of breath, thrombophlebitis, ischemia, congestive heart failure, hypertension, hypertensive reaction, palpitations, orthostatic BP decrease, tachycardia; *CNS:* anxiety, libido decrease, syncope, tremor, seizure, vertigo, Bell's Palsy, paranoia, pituitary apoplexy, increased intraocular pressure, amnesia, hearing loss, neuritis; *Respiratory:* pneumonia, pulmonary nodule, status asthmaticus; *Endocrine:* galactorrhea, hypoadrenalism, diabetes insipidus, gynecomastia, amenorrhea, polymenorrhea, oligomenorrhea, vaginitis; *Urogenital:* nephrolithiasis, hematuria; *Hematologic:* anemia, iron deficiency, epistaxis; *Miscellaneous:* otitis, allergic reaction, increased CK, weight loss.

Evaluation of 20 patients treated for at least 6 months has failed to demonstrate titers of antibodies exceeding background levels. However, antibody titers to Sandostatin were subsequently reported in three patients and resulted in prolonged duration of drug action in two patients. Anaphylactoid reactions, including anaphylactic shock, have been reported in several patients receiving Sandostatin.

OVERDOSAGE

A limited number of accidental overdoses of Sandostatin® in adults have been reported. In adults, the doses ranged from 2,400–6,000 micrograms/day administered by continuous infusion (100-250 micrograms/hour) or subcutaneously (1,500 micrograms t.i.d.). Adverse events in some patients included arrhythmia, hypotension, cardiac arrest, brain hypoxia, pancreatitis, hepatitis steatosis, hepatomegaly, lactic acidosis, flushing, diarrhea, lethargy, weakness, and weight loss.

Sandostatin Injection given in intravenous boluses 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 intravenously over 20 minutes and of 120 mg (120,000 mcg) given intravenously over 8 hours to research patients.

If overdose occurs, symptomatic management is indicated. Up-to-date information about the treatment of overdose can often be obtained from the National Poison Control Center at 1-800-222-1222.

Drug Abuse and Dependence

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

DOSAGE AND ADMINISTRATION

Sandostatin® (octreotide acetate) may be administered subcutaneously or intravenously. Subcutaneous injection is the usual route of administration of Sandostatin for control of symptoms. Pain with subcutaneous administration may be reduced by using the smallest

volume that will deliver the desired dose. Multiple subcutaneous injections at the same site within short periods of time should be avoided. Sites should be rotated in a systematic manner.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration**. Do not use if particulates and/or discoloration are observed.** Proper sterile technique should be used in the preparation of parenteral admixtures to minimize the possibility of microbial contamination. **Sandostatin is not compatible in Total Parenteral Nutrition (TPN) solutions because of the formation of a glycosyl octreotide conjugate which may decrease the efficacy of the product.**

Sandostatin is stable in sterile isotonic saline solutions or sterile solutions of dextrose 5% in water for 24 hours. It may be diluted in volumes of 50-200 mL and infused intravenously over 15-30 minutes or administered by IV push over 3 minutes. In emergency situations (e.g., carcinoid crisis) it may be given by rapid bolus.

The initial dosage is usually 50 mcg administered twice or three times daily. Upward dose titration is frequently required. Dosage information for patients with specific tumors follows.

Acromegaly

Dosage may be initiated at 50 mcg t.i.d. Beginning with this low dose may permit adaptation to adverse gastrointestinal effects for patients who will require higher doses. IGF-I (somatomedin C) levels every 2 weeks can be used to guide titration. Alternatively, multiple growth hormone levels at 0-8 hours after Sandostatin® (octreotide acetate) administration permit more rapid titration of dose. The goal is to achieve growth hormone levels less than 5 ng/mL or IGF-I (somatomedin C) levels less than 1.9 U/mL in males and less than 2.2 U/mL in females. The dose most commonly found to be effective is 100 mcg t.i.d., but some patients require up to 500 mcg t.i.d. for maximum effectiveness. Doses greater than 300 mcg/day seldom result in additional biochemical benefit, and if an increase in dose fails to provide additional benefit, the dose should be reduced. IGF-I (somatomedin C) or growth hormone levels should be re-evaluated at 6-month intervals.

Sandostatin should be withdrawn yearly for approximately 4 weeks from patients who have received irradiation to assess disease activity. If growth hormone or IGF-I (somatomedin C) levels increase and signs and symptoms recur, Sandostatin therapy may be resumed.

Carcinoid Tumors

The suggested daily dosage of Sandostatin during the first 2 weeks of therapy ranges from 100-600 mcg/day in 2-4 divided doses (mean daily dosage is 300 mcg). In the clinical studies, the **median** daily maintenance dosage was approximately 450 mcg, but clinical and biochemical benefits were obtained in some patients with as little as 50 mcg, while others required doses up to 1500 mcg/day. However, experience with doses above 750 mcg/day is limited.

VIPomas

Daily dosages of 200-300 mcg in 2-4 divided doses are recommended during the initial 2 weeks of therapy (range 150-750 mcg) to control symptoms of the disease. On an individual basis, dosage may be adjusted to achieve a therapeutic response, but usually doses above 450 mcg/day are not required.

HOW SUPPLIED

Sandostatin® (octreotide acetate) Injection is available in 1-mL ampuls and 5-mL multi-dose vials as follows:

Ampuls

50 mcg/mL octreotide (as acetate)
Package of 10 ampuls ..... NDC 0078-0180-01

100 mcg/mL octreotide (as acetate)
Package of 10 ampuls ..... NDC 0078-0181-01

500 mcg/mL octreotide (as acetate)
Package of 10 ampuls ..... NDC 0078-0182-01

Multi-Dose Vials

200 mcg/mL octreotide (as acetate)
Box of one ..... NDC 0078-0183-25

1000 mcg/mL octreotide (as acetate)
Box of one ..... NDC 0078-0184-25

Storage

For prolonged storage, Sandostatin ampuls and multi-dose vials should be stored at refrigerated temperatures 2°C-8°C (36°F-46°F) and store in outer carton in order to protect from light. At room temperature, (20°C-30°C or 70°F-86°F), Sandostatin is stable for 14 days if protected from light. The solution can be allowed to come to room temperature prior to administration. Do not warm artificially. After initial use, multiple-dose vials should be discarded within 14 days. Ampuls should be opened just prior to administration and the unused portion discarded. Dispose unused product or waste properly.

*Thomson Healthcare, Inc.

REV: AUGUST 2008 T2009-XX

Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

© Novartis

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Sandostatin LAR safely and effectively. See full prescribing information for Sandostatin LAR.

Sandostatin LAR® Depot (octreotide acetate for injectable suspension)
Initial U.S. Approval: 1988

----------INDICATIONS AND USAGE----------

Sandostatin LAR is a somatostatin analogue indicated for:
Treatment in patients who have responded to and tolerated Sandostatin Injection subcutaneous injection for:

- Acromegaly (1.1)
- Severe diarrhea/flushing episodes associated with metastatic carcinoid tumors (1.2)
- Profuse watery diarrhea associated with VIP-secreting tumors (1.3)

----------DOSAGE AND ADMINISTRATION----------

Patients not currently receiving Sandostatin Injection subcutaneously:

- Acromegaly: 50 mcg three times daily Sandostatin Injection subcutaneously for 2 weeks followed by Sandostatin LAR 20 mg intragluteally every 4 weeks for 3 months (2.1)
- Carcinoid Tumors and VIPomas: Sandostatin Injection subcutaneously 100-600 mcg/day in 2-4 divided doses for 2 weeks followed by Sandostatin LAR 20 mg every 4 weeks for 2 months (2.2)

Patients currently receiving Sandostatin Injection subcutaneously:

- Acromegaly: 20 mg every 4 weeks for 3 months (2.1)
- Carcinoid Tumors and VIPomas: 20 mg every 4 weeks for 2 months (2.2)

Renal Impairment, patients on dialysis: 10 mg every 4 weeks (2.3)
Hepatic Impairment, patients with cirrhosis: 10 mg every 4 weeks (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Vials: 10 mg per 5 mL, 20 mg per 5 mL or 30 mg per 5 mL (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Gallbladder abnormalities may occur. Monitor periodically. (5.1)
- Glucose Metabolism: Hypoglycemia or hyperglycemia may occur. Glucose monitoring is recommended and antidiabetic treatment may need adjustment. (5.2)
- Thyroid Function: Hypothyroidism may occur. Monitor thyroid levels periodically. (5.3)
- Cardiac Function: Bradycardia, arrhythmia or conduction abnormalities may occur. Use with caution in at-risk patients. (5.4)

----------ADVERSE REACTIONS----------

The most common adverse reactions, occurring in ≥20% of patients are:

- Acromegaly: diarrhea, cholelithiasis, abdominal pain, flatulence (6.1)
- Carcinoid Syndrome: back pain, fatigue, headache, abdominal pain, nausea, dizziness (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

The following drugs require monitoring and possible dose adjustment when used with Sandostatin LAR: cyclosporine, insulin, oral hypoglycemic agents, beta-blockers, bromocriptine (7)

See 17 for PATIENT COUNSELING INFORMATION
Revised: xx/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Sandostatin LAR Depot 10 mg, 20 mg and 30 mg is indicated in patients in whom initial treatment with Sandostatin Injection has been shown to be effective and tolerated.

1.1 Acromegaly

Long-term maintenance therapy in acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option. The goal of treatment in acromegaly is to reduce GH and IGF-1 levels to normal [*see Clinical Studies (14)* and *Dosage and Administration (2)*].

1.2 Carcinoid Tumors

Long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors.

1.3 Vasoactive Intestinal Peptide Tumors (VIPomas)

Long-term treatment of the profuse watery diarrhea associated with VIP-secreting tumors.

1.4 Important Limitations of Use

In patients with 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.

2 DOSAGE AND ADMINISTRATION

- Sandostatin LAR Depot should be administered by a trained health care provider. It is important to closely follow the mixing instructions included in the packaging. Sandostatin LAR Depot must be administered immediately after mixing.
- **Do not directly inject diluent without preparing suspension.**
- Sandostatin LAR Depot should be administered intragluteally at 4-week intervals. Administration of Sandostatin LAR Depot at intervals greater than 4 weeks is not recommended.
- Injection sites should be rotated in a systematic manner to avoid irritation. Deltoid injections should be avoided due to significant discomfort at the injection site when given in that area.
- **Sandostatin LAR Depot should never be administered intravenously or subcutaneously.**

The following dosage regimens are recommended.

2.1 Acromegaly

Patients Not Currently Receiving Octreotide Acetate

Patients not currently receiving octreotide acetate should begin therapy with Sandostatin Injection given subcutaneously in an initial dose of 50 mcg three times daily which may be titrated. Most patients require doses of 100 mcg to 200 mcg three times daily for maximum effect but some patients require up to 500 mcg three times daily.

Patients should be maintained on Sandostatin Injection subcutaneous for at least 2 weeks to determine tolerance to octreotide. 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 below (Patients Currently Receiving Sandostatin Injection).

Patients Currently Receiving Sandostatin 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. After 3 months, dosage may be adjusted as follows:

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

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.

2.2 Carcinoid Tumors and VIPomas

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 as described below (Patients Currently Receiving Sandostatin Injection).

Patients Currently Receiving Sandostatin 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. 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 subcutaneously 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 2 months, dosage may be adjusted as follows:

- If symptoms are adequately controlled, consider a dose reduction 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.
- If symptoms are not adequately controlled, increase Sandostatin LAR Depot 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.
- Dosages higher than 30 mg are not recommended.

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 subcutaneously for a

few days at the dosage they were receiving prior to switching to Sandostatin LAR Depot. When symptoms are again controlled, the Sandostatin Injection subcutaneous can be discontinued.

2.3 Special Populations: Renal Impairment

In patients with renal failure requiring dialysis, the starting dose should be 10 mg every 4 weeks. In other patients with renal impairment, the starting dose should be similar to a nonrenal patient (i.e., 20 mg every 4 weeks) [*see Clinical Pharmacology (12)*].

2.4 Special Populations: Hepatic Impairment – Cirrhotic Patients

In patients with established cirrhosis of the liver, the starting dose should be 10 mg every 4 weeks [*see Clinical Pharmacology (12)*].

3 DOSAGE FORMS AND STRENGTHS

Sandostatin LAR Depot 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.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Cholelithiasis and Gallbladder Sludge

Sandostatin may inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder abnormalities or sludge. Patients should be monitored periodically [*see Adverse Reactions (6)*].

5.2 Hyperglycemia and Hypoglycemia

Octreotide alters the balance between the counter-regulatory hormones, insulin, glucagon, and growth hormone, which may result in hypoglycemia or hyperglycemia. Blood glucose levels should be monitored when Sandostatin LAR treatment is initiated, or when the dose is altered. Antidiabetic treatment should be adjusted accordingly [*see Adverse Reactions (6)*].

5.3 Thyroid Function Abnormalities

Octreotide suppresses the secretion of thyroid-stimulating hormone, which may result in hypothyroidism. Baseline and periodic assessment of thyroid function (TSH, total and/or free T_4) is recommended during chronic octreotide therapy [*see Adverse Reactions (6)*].

5.4 Cardiac Function Abnormalities

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 nonspecific ST-T wave changes. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease. 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 (6)*].

5.5 Nutrition

Octreotide may alter absorption of dietary fats.

Depressed vitamin B_{12} levels and abnormal Schilling 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.

5.6 Monitoring: 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 [*see Dosage and Administration (2.0)*].

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

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

5.7 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 [*see Drug Interactions (7.2)*].

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in practice.

Acromegaly

The safety of Sandostatin LAR in the treatment of acromegaly has been evaluated in three phase 3 studies in 261 patients, including 209 exposed for 48 weeks and 96 exposed for greater than 108 weeks. Sandostatin LAR was studied primarily in a double-blind, cross-over manner. Patients on subcutaneous Sandostatin Injection were switched to the LAR formulation followed by an open-label extension. The population age range was 14-81 years old and 53% were female. Approximately 35% of these acromegaly patients had not been treated with surgery and/or radiation. Most patients received a starting dose of 20 mg every 4 weeks intramuscularly. Dose was up or down titrated based on efficacy and tolerability to a final dose between 10-60 mg every 4 weeks. Table 1 below reflects adverse events from these studies regardless of presumed causality to study drug.

Table 1. Adverse Events Occurring in ≥10% of Acromegalic Patients in the Phase 3 Studies

WHO Preferred Term	Phase 3 Studies (Pooled) Number (%) of Subjects with AE's 10 mg/20 mg/30 mg (n=261) n (%)
Diarrhea	93 (35.6)
Abdominal Pain	75 (28.7)
Flatulence	66 (25.3)

Influenza-Like Symptoms	52 (19.9)
Constipation	46 (17.6)
Headache	40 (15.3)
Anemia	40 (15.3)
Injection Site Pain	36 (13.8)
Cholelithiasis	35 (13.4)
Hypertension	33 (12.6)
Dizziness	30 (11.5)
Fatigue	29 (11.1)

The safety of Sandostatin LAR in the treatment of acromegaly was also evaluated in a postmarketing randomized phase 4 study. 104 patients were randomized to either pituitary surgery or 20 mg of Sandostatin LAR. All the patients were treatment naïve (‘de novo’). Crossover was allowed according to treatment response and a total of 76 patients were exposed to Sandostatin LAR. Approximately half of the patients initially randomized to Sandostatin LAR were exposed to Sandostatin LAR up to 1 year. The population age range was between 20-76 years old and 45% were female, 93% were Caucasian, and 1% Black. The majority of these patients were exposed to 30 mg every 4 weeks. Table 2 below reflects the adverse events occurring in this study regardless of presumed causality to study drug.

Table 2. Adverse Events Occurring in ≥10% of Acromegalic Patients in Phase 4 Study

WHO Preferred Term	**Phase 4 Study SAS LAR N=76 n (%)**	**Phase 4 Study Surgery N=64 n (%)**
Diarrhea	36 (47.4)	2 (3.1)
Cholelithiasis	29 (38.2)	3 (4.7)
Abdominal Pain	19 (25.0)	2 (3.1)
Nausea	12 (15.8)	5 (7.8)
Alopecia	10 (13.2)	5 (7.8)
Injection Site Pain	9 (11.8)	0
Abdominal Pain Upper	8 (10.5)	0
Headache	8 (10.5)	6 (9.4)
Epistaxis	0	7 (10.9)

Gallbladder Abnormalities

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.

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.

Glucose Metabolism - Hypoglycemia/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 [*see Warnings and Precautions (5)*].

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 [*see Warnings and Precautions (5)*].

Cardiac

In acromegalics, sinus bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias developed in 9% of patients during Sandostatin Injection therapy. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease [*see Warnings and Precautions (5)*].

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 3.

Table 3. Number (%) of Acromegalic Patients with Common G.I. Adverse Events

Adverse Event	**Sandostatin Injection S.C. Three Times Daily n=114**		**Sandostatin LAR Depot Every 28 Days n=261**	
	n	%	n	%
Diarrhea	66	(57.9)	95	(36.4)
Abdominal Pain or Discomfort	50	(43.9)	76	(29.1)
Nausea	34	(29.8)	27	(10.3)
Flatulence	15	(13.2)	67	(25.7)
Constipation	10	(8.8)	49	(18.8)
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.

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.

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.

Carcinoid and VIPomas

The safety of Sandostatin LAR in the treatment of carcinoid tumors and VIPomas has been evaluated in one phase 3 study. Study 1 randomized 93 patients with carcinoid syndrome to Sandostatin LAR 10 mg, 20 mg, or 30 mg in a blind fashion or to open-label Sandostatin Injection subcutaneously. The population age range was between 25-78 years old and 44% were female, 95% were Caucasian and 3% Black. All the patients had symptom control on their previous Sandostatin subcutaneous treatment. 80 patients finished the initial 24 weeks of Sandostatin exposure in Study 1. In Study 1, comparable numbers of patients were randomized to each dose. Table 4 below reflects the adverse events occurring in >15% of patients regardless of presumed causality to study drug.

Table 4. Adverse Events Occurring in ≥15% of Carcinoid Tumor and VIPoma Patients in Study 1

	Number (%) of Subjects with AE's (n=93)			
WHO Preferred Term	**Sc N=26**	**10 mg N=22**	**20 mg N=20**	**30 mg N=25**
Abdominal Pain	8 (30.8)	8 (35.4)	2 (10.0)	5 (20.0)
Arthropathy	5 (19.2)	2 (9.1)	3 (15.0)	2 (8.0)
Back Pain	7 (26.9)	6 (27.3)	2 (10.0)	2 (8.0)
Dizziness	4 (15.4)	4 (18.2)	4 (20.0)	5 (20.0)
Fatigue	3 (11.5)	7 (31.8)	2 (10.0)	2 (8.0)
Flatulence	3 (11.5)	2 (9.1)	2 (10.0)	4 (16.0)
Generalized Pain	4 (15.4)	2 (9.1)	3 (15.0)	1 (4.0)
Headache	5 (19.2)	4 (18.2)	6 (30.0)	4(16.0)
Musculoskeletal Pain	4 (15.4)	0	1 (5.0)	0
Myalgia	0	4 (18.2)	1 (5.0)	1 (4.0)
Nausea	8 (30.8)	9 (40.9)	6 (30.0)	6 (24.0)
Pruritus	0	4 (18.2)	0	0
Rash	1 (3.8)	0	3 (15.0)	0
Sinusitis	4 (15.4)	0	1 (5.0)	3 (12.0)
URTI	6 (23.1)	4 (18.2)	2 (10.0)	3 (12.0)
Vomiting	3 (11.5)	0	0	4 (16.0)

Gallbladder Abnormalities

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

Glucose Metabolism - Hypoglycemia/Hyperglycemia

In carcinoid patients, hypoglycemia occurred in 4% and hyperglycemia in 27% of patients treated with Sandostatin LAR Depot [*see Warnings and Precautions (5)*].

Hypothyroidism

In carcinoid patients, hypothyroidism has only been reported in isolated patients and goiter has not been reported [*see Warnings and Precautions (5)*].

Cardiac

Electrocardiograms were performed only in carcinoid patients receiving Sandostatin LAR Depot. 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 Warnings and Precautions (5)*].

Other Clinical Studies Adverse Events

Other clinically significant adverse events (relationship to drug not established) in acromegalic and/or carcinoid syndrome patients receiving Sandostatin LAR Depot were malignant hyperpyrexia, cerebral vascular disorder, rectal bleeding, ascites, pulmonary embolism, pneumonia and pleural effusion.

6.2 Postmarketing Experience

The following adverse reactions have been identified during the postapproval use of Sandostatin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Myocardial infarction has been observed in the postmarketing setting, mainly in patients with cardiovascular risk factors. Hypoadrenalism has been reported in some reports in patients 18 months of age and under.

Additional events reported in the postmarketing setting include anaphylactoid reactions, including anaphylactic shock, cardiac arrest, renal failure, renal insufficiency, convulsions, atrial fibrillation, aneurysm, hepatitis, increased liver enzymes, gastrointestinal hemorrhage, pancreatitis, pancytopenia, thrombocytopenia, arterial thrombosis of the arm, retinal vein thrombosis, intracranial hemorrhage, hemiparesis, paresis, deafness, visual field defect, aphasia, scotoma, status asthmaticus, pulmonary hypertension, diabetes mellitus, intestinal obstruction, peptic/gastric ulcer, appendicitis, creatinine increased, CK increased, arthritis, joint effusion, pituitary apoplexy, breast carcinoma, suicide attempt, paranoia, migraines, urticaria, facial edema, generalized edema, hematuria, orthostatic hypotension, Raynaud’s syndrome, glaucoma, pulmonary nodule, pneumothorax aggravated, cellulitis, Bell’s palsy, diabetes insipidus, gynecomastia, galactorrhea, gallbladder polyp, fatty liver, abdomen enlarged, libido decrease, and petechiae.

7 DRUG INTERACTIONS

7.1 Cyclosporine

Concomitant administration of octreotide injection with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection.

7.2 Insulin and Oral Hypoglycemic Drugs

Octreotide inhibits the secretion of insulin and glucagon. Therefore, blood glucose levels should be monitored when Sandostatin LAR treatment is initiated or when the dose is altered and antidiabetic treatment should be adjusted accordingly.

7.3 Bromocriptine

Concomitant administration of octreotide and bromocriptine increases the availability of bromocriptine.

7.4 Other Concomitant Drug Therapy

Concomitant administration of bradycardia-inducing drugs (e.g., beta-blockers) may have an additive effect on the reduction of heart rate associated with octreotide. Dose adjustments of concomitant medication may be necessary.

Octreotide has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs.

7.5 Drug Metabolism Interactions

Limited published data indicate that somatostatin analogs may decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Reproduction studies have been performed in rats and rabbits at doses up to 16x the highest recommended human dose and have revealed no evidence of harm to the fetus due to octreotide. However, because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed [*see Nonclinical Toxicology (13.2)*].

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and efficacy of Sandostatin LAR Depot in the pediatric population have not been demonstrated.

No formal controlled clinical trials have been performed to evaluate the safety and effectiveness of Sandostatin LAR Depot in pediatric under 6 years of age. In post-marketing report, serious adverse events, including hypoxia, necrotizing enterocolitis, and death, have been reported with Sandostatin use in children, most notably in children under 2 years of age. The relationship of these events to octreotide has not been established as the majority of these pediatric patients had serious underlying co-morbid conditions.

The efficacy and safety of Sandostatin LAR Depot was examined in a single randomized, double-blind, placebo-controlled, six–month pharmacokinetics study in 60 pediatric patients age 6-17 years with hypothalamic obesity resulting from cranial insult. The mean octreotide concentration after 6 doses of 40 mg Sandostatin LAR Depot administered by IM injection every four weeks was approximately 3 ng/ml. Steady-state concentrations was achieved after 3 injections of a 40 mg dose. 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. Efficacy was not demonstrated. 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 adults indications such as acromegaly (22%) or malignant carcinoid syndrome (24%), where Sandostatin LAR Depot was 10 to 30 mg once a month.

.

.

8.5 Geriatric Use

Clinical studies of Sandostatin did not include sufficient numbers of subjects age 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.

8.6 Renal Impairment

In patients with renal failure requiring dialysis, the starting dose should be 10 mg. This dose should be up titrated based on clinical response and speed of response as deemed necessary by the physician. In patients with mild, moderate, or severe renal impairment there is no need to adjust the starting dose of Sandostatin. The maintenance dose should be adjusted thereafter based on clinical response and tolerability as in nonrenal patients [*see Clinical Pharmacology (12)*].

Hepatic Impairment - Cirrhotic Patients

In patients with established liver cirrhosis, the starting dose should be 10 mg. This dose should be up titrated based on clinical response and speed of response as deemed necessary by the physician. Once at a higher dose, patient should be maintained or dose adjusted based on response and tolerability as in any noncirrhotic patients [*see Clinical Pharmacology (12)*].

10 OVERDOSAGE

No frank overdose has occurred in any patient to date. Sandostatin 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 intravenously over 20 minutes and of 120 mg (120,000 mcg) given intravenously 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 intravenously, respectively, of octreotide.

11 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 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:

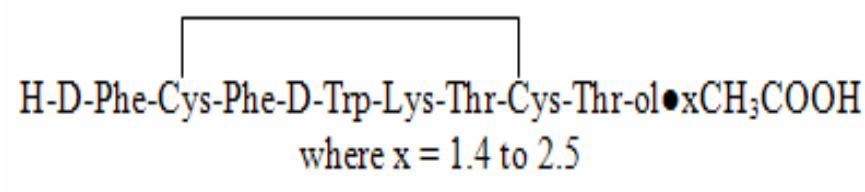
Name of Ingredient	10 mg	20 mg	30 mg
octreotide acetate	11.2 mg*	22.4 mg*	33.6 mg*
D, L-lactic and glycolic acids copolymer	188.8 mg	377.6 mg	566.4 mg

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



12 CLINICAL PHARMACOLOGY

Sandostatin LAR Depot 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 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 4 weeks.

12.1 Mechanism of Action

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).

12.2 Pharmacodynamics

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 and Precautions (5)*].

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

12.3 Pharmacokinetics

Sandostatin Injection

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 three times daily (600 mcg/day). Clearance was reduced by about 66% suggesting nonlinear kinetics of the drug at daily doses of 600 mcg/day 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.

The half-life in renal-impaired patients was slightly longer than normal subjects (2.4-3.1 h versus 1.9 h). The clearance in renal-impaired patients was 7.3-8.8 L/h as compared to 8.3 L/h in healthy subjects. 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).

Patients with liver cirrhosis showed prolonged elimination of drug, with octreotide half-life increasing to 3.7 h and total body clearance decreasing to 5.9 L/h, whereas patients with fatty liver disease showed half-life increasing to 3.4 h and total body clearance of 8.4 L/h. In normal subjects, octreotide half-life is 1.9 h and the clearance is 8.3 L/h which is comparable with the clearance in fatty-liver patients.

Sandostatin LAR Depot

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 biodegration 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.

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 3-5 days to a nadir of <0.01 ng/mL/mg, then slowly increasing and reaching a plateau about 2-3 weeks postinjection. 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 postinjection, 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 postinjection. These plateau concentrations were maintained for nearly 2 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 three times daily 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 4 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 2 injections of 20 mg and 30 mg and after 3 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.

13 NONCLINICAL TOXICOLOGY

13.1 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.

13.2 Reproductive Toxicology Studies

Reproduction studies have been performed in rats and rabbits at doses up to 16x the highest recommended human dose based on body surface area and have revealed no evidence of harm to the fetus due to octreotide.

14 CLINICAL STUDIES

14.1 Acromegaly

The clinical trials of Sandostatin LAR Depot were performed in patients who had been receiving Sandostatin 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.

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 three times daily. 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 [*see Dosage and Administration (2)*]. Growth hormone and IGF-1 were at least as well controlled on Sandostatin LAR Depot as they had been on Sandostatin Injection.

Table 5 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 5. Hormonal Response in Acromegalic Patients Receiving 27 to 28 Injections During[1] Treatment with 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 5, 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 6 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 6. Hormonal Response in Acromegalic Patients Receiving 12 Injections During[1] Treatment with 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 6, 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.

Two open-label clinical studies investigated a 48-week treatment with Sandostatin LAR Depot in 143 untreated (de novo) acromegalic patients. The median reduction in tumor volume was 20.6% in Study 1 (49 patients) at 24 weeks and 24.5% in Study 2 (94 patients) at 24 weeks and 36.2% at 48 weeks.

14.2 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. 67 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 three times daily).

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 6-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 7 presents the average number of daily stools and flushing episodes in malignant carcinoid patients.

Table 7. Average No. of Daily Stools and Flushing Episodes in Patients with Malignant Carcinoid Syndrome

Treatment		Daily Stools (Average No.)		Daily Flushing Episodes (Average No.)	
	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 2-2.5 stools/day).

Mean daily flushing episodes were similar at all doses of Sandostatin LAR Depot and on Sandostatin Injection (approximately 0.5-1 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%).

78 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Sandostatin LAR Depot 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

For prolonged storage, Sandostatin LAR Depot should be stored at refrigerated temperatures between 2°C-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.

17 PATIENT COUNSELING INFORMATION

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.

**Trademark of Thomson Healthcare, Inc.

Sandostatin LAR® Depot vials are manufactured by:

Sandoz GmbH, Schaftenau, Austria

(Subsidiary of Novartis Pharma AG, Basle, Switzerland)

The diluent syringes are manufactured by:

Solvay Pharmaceuticals B.V.

Olst, The Netherlands

Distributed by:

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

T2009-XX

© Novartis