Sandostatin advertisement.

[s.l.]: [s.n.], 1987

SMS 201-995 is now SANDOSTATIN®

INTRODUCING

Sandostatin®

octreotide acetate / SANDOZ

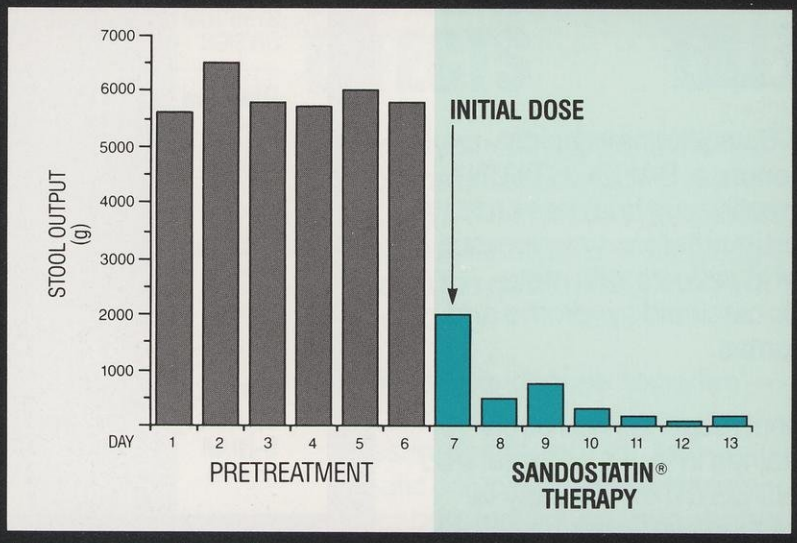
STOPPING POWER

Stopping Symptoms through the Power of Inhibition

TYPICALLY RAPID RESPONSE

Among patients responding to SANDOSTATIN® (octreotide acetate), symptomatic relief is frequently achieved within hours or days.[1,6]

Dramatic drop in stool output upon initiation of SANDOSTATIN® therapy (100 mcg b.i.d.) in a VIPoma patient shows rapid onset of clinical effect



(Adapted from Maton.[6])

WELL TOLERATED

In worldwide clinical experience with SANDOSTATIN® (octreotide acetate), no side effect had an incidence of greater than 10%.[1]

- **The most common adverse reactions, burning at injection site and nausea, were usually mild and transient**
- **SANDOSTATIN® patients have been treated with many other drugs, generally without serious drug interactions**
- **No renal or hematologic toxicity reported**
- **No demonstrated antibody formation**

Patients undergoing chronic SANDOSTATIN® therapy should be periodically monitored for gallbladder disease, thyroid function and fecal fat. See full prescribing information on following page.

NEW

Sandostatin®

octreotide acetate / SANDOZ

***Stopping** Symptoms through the **Power** of Inhibition*

SANDOSTATIN® (octreotide acetate) INJECTION

DESCRIPTION

Sandostatin® (octreotide acetate) Injection, a cyclic octapeptide prepared as a clear sterile solution of octreotide, acetate salt, in buffered sodium chloride for administration by deep subcutaneous (intrafat) 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® (octreotide acetate) Injection is available as sterile 1 mL ampuls in three strengths, containing 0.05, 0.1 or 0.5 mg octreotide (as acetate). Each ampul also contains:

acetic acid, glacial, USP	2.0 mg
sodium acetate trihydrate, USP	2.0 mg
sodium chloride, USP	7.0 mg
water for injection, USP	qs to 1 mL

Acetic acid and sodium acetate trihydrate are added to provide a buffered solution, pH 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:

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol,
x CH_3COOH where x = 1.4 to 2.5

CLINICAL PHARMACOLOGY

Sandostatin® (octreotide acetate) exerts pharmacological actions similar to the natural hormone somatostatin. In normal subjects, it has the ability to suppress secretion of serotonin and the gastroenteropancreatic peptides: gastrin, vasoactive intestinal peptide, insulin, glucagon, secretin, motilin, and pancreatic polypeptide. In addition, Sandostatin® (octreotide acetate) suppresses growth hormone. In animals, Sandostatin® (octreotide acetate) is a more potent inhibitor of growth hormone, glucagon, and insulin release than natural somatostatin with greater selectivity for growth hormone and glucagon suppression. Sandostatin® (octreotide acetate), like somatostatin, decreases splanchnic blood flow.

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

Pharmacokinetics: After subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.5 ng/mL (100 mcg dose) were reached 0.4 hours after dosing. Relative to an equivalent intravenous dose, the bioavailability of a subcutaneous dose was estimated to be 80-135%. This was established based on the respective plasma concentrations determined by a radioimmunoassay, the specificity of which remains to be completely defined. Peak concentrations and area under the curve values were dose proportional both after s.c. or i.v. 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.

The distribution of octreotide from plasma was rapid ($t_{\alpha 1/2}$ = 0.2 h) and the volume of distribution was estimated to be 13.6 L. 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 1.5 hours compared with 1 to 3 minutes with the natural hormone. The duration of action of Sandostatin® (octreotide acetate) 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 patients with severe renal failure requiring dialysis, clearance was reduced to about half that found in normal subjects (from approximately 10 L/h to 4.5 L/h). The effect of hepatic diseases on the disposition of octreotide is unknown.

INDICATIONS AND USAGE

General: Sandostatin® (octreotide acetate) therapy is indicated for control of symptoms in patients with metastatic carcinoid and vasoactive intestinal peptide-secreting tumors (VIPomas).

Data are insufficient to determine whether Sandostatin® (octreotide acetate) decreases the size, rate of growth, or development of metastases in patients with these tumors.

Sandostatin® (octreotide acetate) has been used in patients ranging in age from 1 month to 83 years without any drug limiting toxicity.

Carcinoid Tumors: Sandostatin® (octreotide acetate) 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.

Vasoactive Intestinal Peptide Tumors (VIPomas): Sandostatin® (octreotide acetate) is indicated for the treatment of the profuse watery diarrhea associated with VIP-secreting tumors. Significant improvement has been noted in the overall condition of these otherwise therapeutically unresponsive patients. Therapy with Sandostatin® (octreotide acetate) results in improvement in electrolyte abnormalities, e.g., hypokalemia, often enabling reduction of fluid and electrolyte support.

CONTRAINDICATIONS

Sensitivity to this drug or any of its components.

WARNINGS

Sandostatin® (octreotide acetate) therapy, like the natural hormone, somatostatin, may be associated with cholelithiasis, presumably by altering fat absorption and possibly by decreasing the motility of the gallbladder. Because patients with somatostatinomas have been reported to be at risk for these dysfunctions, patients being treated with Sandostatin® (octreotide acetate) should be monitored periodically for gallbladder disease. Surgical intervention has been required in a few patients who developed severe abdominal pain associated with cholelithiasis while on Sandostatin® (octreotide acetate) therapy.

It is recommended that patients on extended therapy be evaluated periodically using ultrasound evaluations of the gallbladder and bile ducts.

PRECAUTIONS

General: In the treatment of patients with carcinoid syndrome or VIPomas, dosage adjustment may be required to maintain symptomatic control.

Sandostatin® (octreotide acetate) therapy is occasionally associated with mild transient hypo- or hyperglycemia due to alterations in the balance between the counterregulatory hormones; insulin, glucagon, and growth hormone. Patients should be closely observed on introduction of Sandostatin® (octreotide acetate) therapy and at each change of dosage for symptomatic evidence of hyper- or hypoglycemia.

Data on the effect of chronic therapy with Sandostatin® (octreotide acetate) on hypothalamic/pituitary function has not been obtained. A progressive drop in T_4 levels has been reported, culminating in clinical and biochemical hypothyroidism after 19 months of therapy in one clinical trial patient (carcinoid) receiving 1500 mcg of Sandostatin® (octreotide acetate) daily. Therefore, baseline and periodic thyroid function tests using total and free T_4 are advised to monitor patients.

In insulin-dependent diabetics, reduction of insulin requirements may result following initiation of Sandostatin® (octreotide acetate) therapy.

There is evidence that Sandostatin® (octreotide acetate) therapy may alter absorption of dietary fats in some patients. It is suggested that periodic quantitative 72-hour fecal fat and serum carotene determinations be performed to aid in the assessment of possible drug-induced aggravation of fat malabsorption.

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

Because decreased gallbladder contractility and bile stasis may result from treatment with Sandostatin® (octreotide acetate), baseline and periodic ultrasonography may be useful to assess the presence of gallstones *(See WARNINGS)*.

Information for Patients: Careful instruction in sterile subcutaneous injection technique should be given to the patients and to other persons who may administer Sandostatin® (octreotide acetate) 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:

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: Many patients with carcinoid syndrome or VIPomas being treated with Sandostatin® (octreotide acetate) have also been, or are being, treated with many other drugs to control the symptomatology or progression of the disease, generally without serious drug interaction. Included are chemotherapeutic agents, H_2 antagonists, antimotility agents, drugs affecting glycemic states, solutions for electrolyte and fluid support or hyperalimentation, antihypertensive diuretics, and antidiarrheal agents.

Where symptoms are severe and Sandostatin® (octreotide acetate) therapy is added to other therapies used to control glycemic states such as sulfonylureas, insulin, diazoxide and to beta blockers or agents for the control of fluid and electrolyte balance, patients must be monitored closely and adjustment made in the other therapies as the symptoms of the disease are controlled. Evidence currently available suggests these imbalances in fluid and electrolytes or glycemic states are secondary to correction of pre-existing abnormalities and not to a direct metabolic action of Sandostatin® (octreotide acetate). Adjustment of the dosage of drugs, such as insulin, affecting glucose metabolism may be required following initiation of Sandostatin® (octreotide acetate) therapy in patients with diabetes.

Since Sandostatin® (octreotide acetate) has been associated with alterations in nutrient absorption, its effect on absorption of any orally administered drugs should be carefully considered. A single case of transplant rejection episode (renal/whole pancreas) in a patient immunosuppressed with cyclosporine has been reported. Sandostatin® (octreotide acetate) treatment to reduce exocrine secretion and close a fistula in this patient resulted in decreases in blood levels of cyclosporine and may have contributed to the rejection episode.

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® (octreotide acetate). No long-term studies in animals to assess carcinogenicity have been completed. Sandostatin® (octreotide acetate) did not impair fertility in rats at doses up to 1 mg/kg/day.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 30 times the highest human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Sandostatin® (octreotide acetate). 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® (octreotide acetate) is administered to a nursing woman.

Pediatric Use: Experience with Sandostatin® (octreotide acetate) in the pediatric population is limited. The youngest patient to receive the drug was 1 month old. Doses of 1-10 mcg/kg body weight were well tolerated in the young patients. A single case of an infant (nesidioblastosis) was complicated by a seizure thought to be independent of Sandostatin® (octreotide acetate) therapy.

ADVERSE REACTIONS

The incidence of adverse reactions by patient group and in the total cohort (N = 491) of patients follows. These adverse reactions were largely of mild to moderate severity and of short duration.

Adverse Reactions Occurring in 3 to 10% of Patients

Reaction	Number Reporting: Carcinoid and VIPoma Patients N = 211 (%)	Other Patients N = 280 (%)	Total N = 491 (%)
Nausea	16 (7.6)	31 (11.1)	47 (9.6)
Injection Site Pain	16 (7.6)	21 (7.5)	37 (7.5)
Diarrhea	10 (4.7)	24 (8.6)	34 (6.9)
Abdominal Pain/ Discomfort	6 (2.8)	27 (9.6)	33 (6.7)
Loose Stools	3 (1.4)	18 (6.4)	21 (4.3)
Vomiting	4 (1.9)	15 (5.4)	19 (3.9)

Adverse Reactions Occurring in 1 to 3% of Patients

Reaction	Number Reporting: Carcinoid and VIPoma Patients N = 211 (%)	Other Patients N = 280 (%)	Total N = 491 (%)
Headache	3 (1.4)	7 (2.5)	10 (2.0)
Fat Malabsorption	5 (2.4)	3 (1.1)	8 (1.6)
Dizziness/ Light-headedness	3 (1.4)	5 (1.8)	8 (1.6)
Hyperglycemia	3 (1.4)	5 (1.8)	8 (1.6)
Fatigue	2 (0.9)	5 (1.8)	7 (1.4)
Flushing	3 (1.4)	4 (1.4)	7 (1.4)
Hypoglycemia	1 (0.5)	5 (1.8)	6 (1.2)
Edema	2 (0.9)	3 (1.1)	5 (1.0)
Asthenia/Weakness	4 (1.9)	1 (0.4)	5 (1.0)
Injection Site/ Wheal/Erythema	4 (1.9)	1 (0.4)	5 (1.0)

In addition, the following infrequent reactions were reported (fewer than 1% of patients):

Gastrointestinal: Constipation, flatulence, hepatitis, jaundice, slight increase in liver enzymes, rectal disorder (spasm), GI bleeding, stomach swollen, heartburn, fluttering sensation, abnormal stools, and cholelithiasis.

Integumentary: Hair loss, thinning of skin, skin flaking, bruising, bleeding from a superficial wound, pruritus, and rash.

Musculoskeletal: Backache pain, muscle pain, muscle cramping, joint pain, shoulder and leg pain, leg cramps, and chest pain.

Cardiovascular: Shortness of breath, hypertensive reaction, thrombophlebitis, ischemia, congestive heart failure, hypertension, palpitations, orthostatic BP decrease, and chest pain.

CNS: Anxiety, anorexia, convulsions, depression, drowsiness, vertigo, hyperesthesia, pounding in head, insomnia, irritability, libido decrease/frigidity, forgetfulness, malaise, nervousness, shakiness, syncope, tremor, and Bells' Palsy.

Respiratory: Rhinorrhea

Endocrine: Galactorrhea

Clinical hypothyroidism requiring thyroid hormone replacement was observed after 19 months of therapy with 1500 mcg daily of Sandostatin® (octreotide acetate) in a clinical trial patient. A progressive fall to low total and free T_4 values was observed, without an elevated TSH, indicative of hypothalamic-pituitary dysfunction, probably related to Sandostatin® (octreotide acetate) therapy.

Urogenital: Oliguria, pollakiuria, prostatitis, and urine hyperosmolarity.

Autonomic: Burning sensation, dry mouth, numbness, hyperhidrosis, hyperdipsia, warm feeling, and visual disturbance.

Miscellaneous: Chills, fever, throat discomfort, increased CPK, arm pain, and eyes burning.

Evaluation of 20 patients treated for at least 6 months has failed to demonstrate titers of antibodies exceeding background levels.

OVERDOSAGE

Specific information on Sandostatin® (octreotide acetate) overdosage is not available as no frank overdosage has occurred in any patient to date. Bolus i.v. injections of 1000 mcg given to healthy volunteers have been tolerated without serious complication.

Based on the pharmacological properties of Sandostatin® (octreotide acetate), acute overdosage may be expected to produce hyper- or hypoglycemia, depending on the endocrine status of the patient and type of peptide-secreting tumor involved. Hyper- and hypoglycemia may be manifested by neurologic and mental disturbances such as loss of sensory or motor function, incoordination, visual blurring, dizziness, drowsiness, and disturbed consciousness. These conditions should resolve with temporary withdrawal of the drug and symptomatic treatment.

The i.v. LD_{50} is 72 mg/kg in mice and 18 mg/kg in rats.

DOSAGE AND ADMINISTRATION

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.**

Subcutaneous injection is the recommended route of administration of Sandostatin® (octreotide acetate) for control of symptoms in most instances. Intravenous bolus injections have been used under emergency conditions. Multiple injections at the same site within short periods of time should be avoided. The initial dosage is 50 mcg, administered subcutaneously, once or twice daily. Thereafter, the number of injections and dosage may be increased gradually based on patient tolerability and response. Dosage information for patients with specific tumors follows. The drug is usually given in a b.i.d. or t.i.d. schedule.

Carcinoid Tumors: The suggested daily dosage of Sandostatin® (octreotide acetate) during the first two weeks of therapy ranges from 100 to 600 mcg per day in two to four 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 per day. However, experience with doses above 750 mcg per day is limited.

VIPomas: Daily dosages of 200 to 300 mcg in two to four divided doses are recommended during the initial 2 weeks of therapy (range 150 to 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 per day are not required.

HOW SUPPLIED

Sandostatin® (octreotide acetate) Injection is available as a one mL ampul in packages of 20 and 50 as follows:

0.05 mg octreotide (as acetate)
Package of 20 ampuls (NDC 0078-0180-03)
Package of 50 ampuls (NDC 0078-0180-04)

0.1 mg octreotide (as acetate)
Package of 20 ampuls (NDC 0078-0181-03)
Package of 50 ampuls (NDC 0078-0181-04)

0.5 mg octreotide (as acetate)
Package of 20 ampuls (NDC 0078-0182-03)
Package of 50 ampuls (NDC 0078-0182-04)

Sandostatin® (octreotide acetate) is also available as a patient home administration starter kit containing an ampul opener, alcohol swabs and the following one mL drug ampuls:

0.05 mg octreotide (as acetate)
Package of 30 ampuls (NDC 0078-0180-15)

0.1 mg octreotide (as acetate)
Package of 30 ampuls (NDC 0078-0181-15)

0.5 mg octreotide (as acetate)
Package of 18 ampuls (NDC 0078-0182-17)

Storage: For prolonged storage, Sandostatin® (octreotide acetate) ampuls should be stored in the refrigerator at 2°-8°C (36°-46°F). Ampuls can be stored at room temperature (20°-30°C or 70°-86°F) for the day they will be used. [JANUARY 1, 1989 SDS-Z1]

Manufactured by Sandoz, Ltd., Basle, Switzerland
for SANDOZ Pharmaceuticals Corporation, East Hanover, NJ 07936

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