Sandostatin LAR® Depot (octreotide acetate for injectable suspension)

Caution: Federal law prohibits dispensing without a prescription.

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-(hydroxymethyl) 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 biodegradeable 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 vial of diluent contains:

carboxymethylcellulose sodium	10.0 mg
mannitol	12.0 mg
water for injection	2.0 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:

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol·xCH_3COOH

where x = 1.4 to 2.5

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® (octreotide acetate) Injection with the added feature of slow release of octreotide from the site of injection, reducing the need for frequent administration. This slow release occurs as the polymer biodegrades, primarily through hydrolysis. Sandostatin LAR® Depot is designed to be injected intramuscularly (intragluteally) once every four weeks.

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

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

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

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

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

Pharmacokinetics

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

1. Pharmacokinetics of octreotide acetate

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

In healthy volunteers the distribution of octreotide from plasma was rapid ($t\alpha_{½}$ = 0.2 h), the volume of distribution (Vdss) was estimated to be 13.6 L and the total body clearance was 10 L/h.

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

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

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

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

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

2. Pharmacokinetics of Sandostatin LAR® Depot

After a single i.m. injection of the long acting depot dosage form Sandostatin LAR® Depot in healthy volunteer subjects, the serum octreotide concentration reached a transient initial peak of about 0.03 ng/mL/mg within 1 hour

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

In patients with acromegaly, the octreotide concentrations after single doses of 10 mg, 20 mg, and 30 mg Sandostatin LAR® Depot were dose proportional. The transient day 1 peak, amounting to 0.3 ng/mL, 0.8 ng/mL, and 1.3 ng/mL, respectively, was followed by plateau concentrations of 0.5 ng/mL, 1.3 ng/mL, and 2.0 ng/mL, respectively, achieved about 3 weeks post injection. These plateau concentrations were maintained for nearly 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 i.m. every 4 weeks the peak-to-trough variation in octreotide concentrations ranged from 44% to 68%, compared to the 163% to 209% variation encountered with the daily subcutaneous t.i.d. regimen of Sandostatin® Injection solution.

In patients with carcinoid tumors, the mean octreotide concentrations after 6 doses of 10 mg, 20 mg, and 30 mg Sandostatin LAR® Depot administered by i.m. injection every four weeks were 1.2 ng/mL, 2.5 ng/mL, and 4.2 ng/mL, respectively. Concentrations were dose proportional and steady-state concentrations were reached after 2 injections of 20 and 30 mg and after three injections of 10 mg.

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

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

CLINICAL TRIALS

The clinical trials of Sandostatin LAR® Depot 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.

Acromegaly

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

In two of the clinical trials, a total of 101 patients were entered who had, in most cases, achieved a GH level < 5 ng/mL on Sandostatin® Injection given in doses of 100 mcg or 200 mcg t.i.d. Most patients were switched to 20 mg or 30 mg doses of Sandostatin LAR® Depot given once every 4 weeks for up to 27 to 28 injections. A few patients received doses of 10 mg and a few required doses of 40 mg. GH and IGF-I 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, 20 or 30 mg every 4 weeks, depending upon the degree of GH suppression. (The recommended regimen for these dosage changes is described under **Dosage and**

Administration). GH and IGF-I were at least as well-controlled on Sandostatin LAR® Depot as they had been on Sandostatin® Injection.

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

Table 1

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

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

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

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

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

Table 2

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

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

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

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