Drug Monograph

A - Drug Name

octreotide

SYNONYM(S): SMS 201-995; somatostatin analogue

COMMON TRADE NAME(S): Sandostatin® (Novartis); Sandostatin® LAR™ (Novartis)

back to top

B - Mechanism of Action and Pharmacokinetics

Octreotide is a synthetic octapeptide analog of somatostatin, ofwith similar effects, but a prolonged duration of action. Its major effects include inhibition of the release of pituitary growth hormone. Octreotide also suppresses the secretion of serotonin and the endocrine secretions of the pancreas, stomach, and intestine (including gastrin, vasoactive intestinal peptide, insulin, glucagon, secretin, motilin, pancreatic polypeptide and TRH stimulated release of TSH). The inhibition of gut hormones by octreotide acts to slow gastrointestinal transit time, and regulate water and electrolyte transport across the gut. This likely explains the symptomatic benefit derived from this drug in patients with carcinoid syndrome and VIPomas (vasoactive intestinal peptide-secreting tumours). Octreotide also decreases splanchnic blood flow.

Absorption	Oral: Poorly absorbed from gastrointestinal tract
Distribution	SC: Completely and rapidly absorbed after injection. Peak levels are reached within 30 minutes. No significant accumulation after repeated SC administration. IM (LAR): Transient initial peak within 1 hour after administration, then decrease to undetectable levels within 24 hours and for the next 7 days. Concentration increases and plateaus (to a level higher than the initial peak) around day 14, and is maintained for the following 3-4 weeks. Steady state is achieved after 2 injections of 20 and 30 mg in patients with carcinoid tumours. Cross blood brain barrier? no information found

	PPB	65 %
Metabolism	Slowly catabolized to inactive fragments. Octreotide LAR concentration decreases slowly, with terminal degradation of the polymer matrix dosage form.	
	Active metabolites	no information found
	Inactive metabolites	yes
Elimination	Mainly by kidneys.	
	Urine	32% is excreted unchanged.
	Half-life	t ½ α = SC: 100 min, IV: 90 min

back to top

C - Indications and Status

Health Canada Approvals:

- Symptomatic metastatic carcinoid syndrome
- Symptomatic vasoactive intestinal peptide-secreting tumor (VIPoma)
- Acromegaly
- Prevention of complications following pancreatic surgery
- Bleeding gastroesophageal varices

Other Uses:

- Other neuroendocrine tumours
- Management of severe diarrhea not responsive to other measures
- Management of chronic bowel obstruction due to advanced cancer

back to top

D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Auditory	Tinnitus	E
Cardiovascular	Arrhythmia	I
	Arterial thromboembolism (rare)	E
	Bradycardia	I
	Chest pain (<1%)	I
	Conduction disorder	I
	Flushing (<1%)	E
	Hypertension (<1%)	I
	Other (ischemic attack)	I
	QT interval prolonged	I
	Venous thromboembolism (rare)	E
Dermatological	Alopecia (4%)	E
	Other (4%) (acne)	E
	Pruritus (4%)	E
	Purpura (4%)	I
	Urticaria (4%)	E
Gastrointestinal	Abdominal pain (44%)	E
	Constipation (9%)	E
	Diarrhea (58%)	I
	Dry mouth (<1%)	E
	Flatulence (13%)	E
	GI hemorrhage (rare)	E
	Mucositis (<2%)	E
	Nausea (30%)	I
	Other (B12 malabsorption)	E
	Steatorrhea	E
	Vomiting (4%)	I
	Weight changes	I
General	Edema (1%)	E
	Fatigue (10%)	I E
	Fever (2%)	I E

	Flu-like symptoms (6%)	I E
Hepatobiliary	Bilary tract disorders (63%) (stones 24%; cholangitis- rare)	D
	Cholecystitis (rare)	D
	Cholestasis (rare)	D
	Hepatitis (<2%)	E
	↑ LFTs	E
	Pancreatitis (rare)	I E
Hypersensitivity	Anaphylaxis (rare)	I
Infection	Infection (4%)	I E
Injection site	Injection site reaction (8%) (pain, redness, swelling)	I
Metabolic / Endocrine	Hyperglycemia	E
	Hypoglycemia (<2%)	E
	Hypothyroidism	D
	Other (increased zinc [if on TPN])	E
Musculoskeletal	Arthralgia	E
	Muscle cramps (4%)	E
	Other (osteonecrosis)	E L
	↑CPK	E
Nervous System	Anxiety (<1%)	I
	Depression (<1%)	E
	Dizziness (2%)	E
	Headache (2%)	E
	Neuropathy (rare)	E
	Seizure (<1%)	I
	Sleep disorder (<1%)	I
	Syncope (<1%)	I
	Vertigo	E
Ophthalmic	Eye disorders (visual disturbances)	I
Respiratory	Epistaxis (<2%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.
Dose-limiting side effects are underlined.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)

D = *delayed* (weeks to months) L = *late* (months to years)

Local reactions include pain and the sensations of stinging, tingling or burning at the site of injection with redness and swelling. These rarely last more than 15 minutes and may decrease in frequency and severity with continued use. Local discomfort may be reduced by allowing the solution to reach room temperature before injection and by slowly injecting octreotide.

Gastrointestinal side effects generally develop during the first days to weeks of treatment and diminish with time; however, some cases may be severe and require drug discontinuation. They may be reduced by avoiding meals around the time of octreotide administration (i.e. timing injections between meals or at bedtime). Steatorrhea occurs commonly in carcinoid syndrome patients at dosages of 500 mcg tid. A reduction in dietary fat may minimize some of the adverse GI effects

back to top

E - Dosing

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Sudden breakthroughs from symptomatic control may occur infrequently, with rapid recurrence of severe symptoms, in which dose adjustment may be required. Response should be monitored (plasma 5-HIAA, serotonin, substance P, VIP etc).

Adults:

Dose should be gradually titrated according to the disease and response.

Octreotide (short acting): Subcutaneous

- Starting dose: 50 µg sc daily or bid
- Carcinoid: 100-600 µg/day in 2-4 divided doses
- VIPomas: 200-300 µg/day in 2-4 divided doses

Octreotide LAR (long acting): IM

Once symptoms controlled on octreotide (short acting), patients may be switched to the LAR IM preparation, but octreotide (short acting) SC should be continued for at least 2 weeks to prevent recurrence of symptoms. Breakthrough symptoms while on LAR IM preparation can be controlled with short term SC octreotide (short acting) if necessary.

- Starting dose: 20 mg IM every 4 weeks
- After 2 months may be decreased to 10 mg or increased to 30 mg depending on response

Dosage with Toxicity:

Dosage in myelosuppression: No adjustment required

Dosage with Hepatic Impairment:

Half-life is prolonged in patients with cirrhosis; dose adjustment may be required.

Dosage with Renal Impairment:

Clearance can be decreased by 50% in severe renal failure requiring dialysis; therefore dosage adjustment may be necessary, but no details found.

Dosage in the elderly:

Dose adjustments may be necessary due to decreased clearance in elderly patients.

Children:

Limited data are available regarding usage in pediatric populations. Poor growth has been reported in some pediatric patients on > 1 year of octreotide treatment; however, “catch-up” growth has occurred after drug discontinuation.

back to top

F - Administration Guidelines

- Keep refrigerated; protect from light.

Short Acting (sc ampoules or multidose vials):

- Subcutaneous self-administration (or administered by home caregiver); drug available by outpatient prescription.
- Rotate injection sites; multiple SC injections at the same site within short periods of time should be avoided.
- For day-to-day use, may be stored at room temperature for up to 2 weeks, protected from light. Open ampoule(s) just prior to administration and discard unused portion
- Incompatible in TPN solutions.
- For IV infusion (emergency treatment for carcinoid syndrome only): further dilute in NS (preferred) or D5W.

Long Acting (ie. Sandostatin LAR®):

- May only be administered by deep intragluteal injection
- To be injected at doctor's office or cancer centre. Drug available by outpatient prescription.
- Alternate between left and right gluteal muscles for subsequent injections.
- Vials can remain at room temperature, protected from light, on the day of the injection
- Reconstitute with supplied diluent as directed. Suspension must be prepared immediately before IM injection.
- Patients switching over to the long-acting injection may need to continue to receive SC octreotide (short acting) for approximately 2 weeks, and some individuals may need additional rescue SC octreotide (short acting) for up to 2 to 3 months because of the time required to reach steady-state octreotide levels, as the drug is slowly released from the microspheres.

back to top

G - Special Precautions

Other:

Octreotide is contraindicated in patients with hypersensitivity to octreotide or to any component of the formulation.

In **insulin dependent diabetics**, reduction of insulin requirements may result following initiation of octreotide therapy.

Octreotide is not mutagenic but is **carcinogenic** in animal models. Its safety in **pregnancy** or effects on **fertility** has not been established, although no effects have been seen in animals. **Breast feeding** is not recommended since octreotide can be secreted into animal milk.

back to top

H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Diazoxide, Sulfonylureas, Beta-blockers, Insulin	Altered effect on blood sugar	Transient hyper- or hypoglycemia caused by octreotide	Monitor blood sugar

Oral cyclosporine	↓ cyclosporine serum levels	Delayed intestinal absorption of cyclosporine	Monitor serum levels of cyclosporine; adjust oral cyclosporine dose or use IV
Drugs metabolised by CYP 450 (terfenadine etc)	↑ effect of concomitant drugs	Somatostatin inhibits metabolism via CYP 450	Caution; especially for drugs with low therapeutic index
Drugs prolonging QT (droperidol, sparfloxacin, etc)		Additive effects	Avoid concomitant usage
cimetidine	↓ serum levels	Delayed intestinal absorption of cimetidine	Caution
bromocriptine	↑ bioavailability of bromocriptine	Unknown	Caution

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Serum blood glucose, especially in diabetic patients	Baseline and periodic
Ultrasonograph of the gall bladder and bile ducts, to assess the presence of gallstones	(during long-term therapy, every 6 to 12 months)
Clinical toxicity assessment (including GI, hepatobiliary)	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Monitoring of zinc levels in patients on TPN, as serum zinc may rise excessively with reversal of fluid loss	Periodic
Assessment of fat malabsorption and vitamin B12 levels with long term use	Periodic
Thyroid function tests, with long term usage	Baseline and periodic

back to top

J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

back to top

K - References

Cancer Drug Manual (the Manual), 1994, British Columbia Cancer Agency (BCCA)

Octreotide: e-AHFS Drug Information. Accessed July 8, 2009.

Product Monograph: Sandostatin® and Sandostatin® LAR (octreotide). Novartis Pharmaceuticals, Canada, December 19, 2008.

August 2016 edited indications

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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back to top