Drug Monograph

A - Drug Name

lanreotide

COMMON TRADE NAME(S): Somatuline® Autogel®

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B - Mechanism of Action and Pharmacokinetics

Lanreotide is a synthetic analogue of somatostatin, an endogenous peptide with high affinity for somatostatin type 2 and type 5 receptors found in the pituitary gland, pancreas and growth hormone-secreting pituitary tumours. Somatostatin analogues inhibit cell proliferation via direct anti-tumour effects from activation of somatostatin receptors on tumour cells and indirect effects via inhibition of mitogenic growth factors, such as insulin-like growth factor and inhibition of tumour angiogenesis.

Absorption	Population pharmacokinetics in patients with neuroendocrine tumours showed rapid initial release of lanreotide within the first day after injection. Steady state concentrations were reached after 4 to 5 injections of 120 mg every 4 weeks and were sustained up to 96 weeks after the first injection.	
Distribution	Intravenous administration shows limited extravascular distribution.	
	PPB	79-83%
Metabolism	Extensive metabolism in the GI tract after biliary excretion.	
Elimination	Urine	< 1% after a single dose of 3 mg SC
	Feces	< 0.5% of administered dose over 24 hrs at steady state

Half-life	28-36 days

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C - Indications and Status

Health Canada Approvals:

- Enteropancreatic neuroendocrine tumours (NETs)
- Carcinoid syndrome

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Not applicable

Extravasation Potential: None

The following adverse effects includes those reported with a frequency ≥ 5% in clinical trials in enteropancreatic NETs patients administered lanreotide every 4 weeks, where the incidence was greater than placebo by ≥ 2%, as well severe or life-threatening events from other trials.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Auditory	Hearing impaired (1- <5%, permanent; carcinoid patients)	E D
Cardiovascular	Bradycardia (rare)	E
	Hypertension (13%)	E
Dermatological	Rash (5%)	E
Gastrointestinal	Abdominal pain (24%)	E
	Dehydration (5%)	E
	Nausea, vomiting (19%)	I E
General	Fatigue (8%)	E
Hematological	Anemia (1 to <5%; carcinoid patients)	D

Hepatobiliary	Biliary tract disorders (14%) (cholelithiasis; rare - cholecystitis)	E D
	Hepatic failure (rare)	E D
	Other (6%) (pancreatic insufficiency - 6%)	E
	Pancreatitis (rare)	D
Hypersensitivity	Hypersensitivity / anaphylaxis	I
Injection site	Injection site reaction (8%) (pain)	I E
Metabolic / Endocrine	Hyperglycemia (7%) /diabetes	E
	Hypoglycemia (rare)	E
	Hypothyroidism (rare, observed in acromegaly)	E D
Musculoskeletal	Musculoskeletal pain (10%)	E
Nervous System	Dizziness (9%)	E
	Headache (16%)	E
	Syncope (rare)	E
Respiratory	Cough, dyspnea (6%)	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.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for lanreotide include abdominal pain, nausea, vomiting, headache, biliary tract disorders, hypertension, and musculoskeletal pain.

Patients with cardiac disorders may experience **sinus bradycardia**; heart rate should be monitored.

Lanreotide inhibits the secretion of insulin and glucagon and may result in changes to blood glucose levels, including **hypo or hyperglycemia**. Blood glucose levels should be monitored, especially in diabetic patients.

Lanreotide may reduce gallbladder motility leading to **cholelithiasis**.

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E - Dosing

Refer to protocol by which patient is being treated.

If patients are being treated with lanreotide for enteropancreatic NETs, do not give an additional dose for the treatment of carcinoid syndrome.

Adults:

Enteropancreatic NETs or Carcinoid Syndrome:

Subcutaneous: 120 mg Every 4 weeks

Dosage with Toxicity:

No dosage adjustment required. The drug should be discontinued in the case of disease progression or severe adverse events.

Dosage with Hepatic Impairment:

Lanreotide clearance is reduced by 30% in patients with moderate to severe hepatic impairment. Patients with neuroendocrine tumours or carcinoid tumours and hepatic impairment have not been studied.

Hepatic Impairment	Lanreotide Dose
Mild (Child-Pugh A)	Use with caution as no data
Moderate to severe (Child-Pugh B or C)	Use with caution as no data*

*in acromegaly, a starting dose of 60 mg is recommended followed by dose adjustments.

Dosage with Renal Impairment:

Lanreotide clearance was not affected in patients with neuroendocrine tumours and mild or moderate renal impairment. Patients with carcinoid syndrome and renal impairment have not been studied.

Renal Impairment (CrCl in mL/min)	Enteropancreatic NET Dose (mg)	Carcinoid Syndrome Dose (mg)
Mild (CrCl ≥ 60)	120	Use with caution as no data
Moderate (CrCl 30 to <60)	120	Use with caution as no data*
Severe (CrCl < 30)	Use with caution as no data*	Use with caution as no data*

*in acromegaly, a starting dose of 60 mg is recommended followed by dose adjustments.

Dosage in the elderly:

No specific dose adjustment has been recommended.

Increases in half-life and mean residence time were observed in healthy subjects over 65 years of age, with no change in either AUC or Cmax. No effect of age on clearance and volume of distribution was observed in pharmacokinetics analysis with NET patients aged 65-85 years.

Clinical studies did not include sufficient number of patients aged ≥ 65 years with carcinoid syndrome or enteropancreatic NETs to evaluate whether they respond differently from younger patients.

Children:

Lanreotide has not been studied in pediatric patients.

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F - Administration Guidelines

- The drug is for immediate and single use after first opening. No reconstitution is required.
- Lanreotide should be injected by deep subcutaneous route in the superior external quadrant of the buttock or upper outer thigh.
- In the case of self-administration (with appropriate training), the injection may be given in the upper outer thigh.
- The skin should be stretched prior to injection and the injection site should be alternated between right and left sides.
- Typically 20 seconds are needed to complete each injection.
- If a dose is missed, the next dose should be administered as soon as possible.
- The drug should be stored under refrigeration (2-8^{o}C) in its original package.
- The drug may be stored at room temperature for 30 minutes before administration. Keep pouch sealed until just prior to injection.

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or any ingredients in the formulation
- Patients who are hypersensitive to somatostatin or related peptides
- Patients with complicated, untreated lithiasis of the bile ducts

Other Warnings/Precautions:

- Use with caution and monitor blood glucose closely in patients with diabetes
- Exercise caution when driving or operating machinery while on treatment, as headache and dizziness were most commonly reported.

Other Drug Properties:

- Carcinogenicity: Documented in animals
  An increased incidence of subcutaneous tumours at injection sites was observed in animals given daily injections. These findings may not be clinically relevant in humans receiving monthly injections.

Pregnancy and Lactation:

- Fetotoxicity: Yes
- Teratogenicity: Unlikely
  Lanreotide is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **6 months** after the last dose (general recommendation).

- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Probable
  May reduce fertility in females

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H - Interactions

Lanreotide is extensively metabolized in the GI tract after biliary excretion and may reduce intestinal absorption of co-administered drugs.

Limited data indicate that somatostatin analogues may decrease metabolic clearance of drugs metabolized by CYP450 enzymes.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Bradycardia-inducing drugs (e.g. beta-blockers)	↓ heart rate	Additive	Dose adjustment of concomitant drugs may be necessary
Cyclosporine (oral)	↓ bioavailability of cyclosporine by ~20%	Delayed intestinal absorption of cyclosporine	Monitor serum levels of cyclosporine and adjust the cyclosporine dose as needed or switch to IV cyclosporine
Bromocriptine	↑ bioavailability of bromocriptine	altered bromocriptine absorption	Caution and monitor for bromocriptine toxicity; consider bromocriptine dose reduction
Hypoglycemic agents (e.g. insulin, sulfonylureas)	↑ risk of hypoglycemia	Additive	Caution, monitor and adjust dose of hypoglycemic agent as required
CYP3A4 substrates with a low therapeutic index (e.g. sirolimus, tacrolimus)	↑ substrate exposure	lanreotide may reduce clearance (theoretical)	Caution & monitor; consider substrate dose reduction

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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
Blood glucose	Baseline and at each visit; more frequent in diabetic patients
Heart rate	Baseline and at each visit; more frequent in patients with cardiac disorders
Gallbladder ultrasound	Baseline and periodic
Thyroid function	As clinically indicated
Clinical toxicity assessment for GI effects, injection site reactions, CNS effects, hypertension	At each visit

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

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- lanreotide

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K - References

Caplin ME, Pavel M, Ćwikła JB, et al; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014 Jul 17;371(3):224-33.

Lanreotide: Drug information. Lexicomp. Accessed June 12, 2017.

Product monograph: Somatuline® Autogel® (lanreotide injection). Ipsen Biopharmaceuticals Canada Inc. Aug 8, 2023.

May 2024 Modified Pharmacokinetics, Dosage in hepatic impairment, Dosage in renal impairment, Dosage in the elderly, Administration guidelines, Pregnancy/lactation, and Interactions sections

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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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