



Insulin Glargine (Lantus®)

What is insulin glargine (Lantus®)?

Lantus is the latest insulin product to be marketed in Canada. It is a human insulin analog produced by recombinant DNA technology.¹ This product is the only insulin available with a 24-hour duration and a peak-less profile after subcutaneous administration.²

Pharmacodynamics?²

The replacement of three amino acids in the human insulin molecule shifts the isoelectric point, producing a solution that is completely soluble at pH 4. When injected into the subcutaneous tissue, which has a physiological pH of 7.4, the acidic solution is neutralized. This leads to the formation of microprecipitates, or stabilized aggregates, from which small amounts of Lantus are slowly released. The slow dissolution of free hexamers results in the lack of a pronounced peak which allows insulin glargine to be dosed once daily.

For whom is insulin glargine approved?

In Canada, Lantus® is officially approved for once daily subcutaneous administration in patients over 17 years old with Type 1 or Type 2 diabetes mellitus.³ It is approved for children 6 years of age and older in the United States and Europe.

The place of insulin glargine in diabetes therapy has not yet been clearly defined. However, it appears to be a practical alternative for patients:

- i. not achieving glycemic control with NPH insulin;
- ii. experiencing frequent symptomatic hypoglycemia;
- iii. with erratic schedules, lifestyles.

What are the usual dosing regimens?³

Initiation: Insulin-naïve patients (kids and adults) should start with 10 IU OD and this dose should be adjusted according to the patient response. The standard dosing range is 2 –100 IU per day. It may take 2 – 4 days to reach steady levels over 24 hours.

Changing over from NPH or Ultralente: OD dosage regimens can use the same daily amount of insulin glargine (unit for unit). When switching from a BID NPH regimen to glargine, decrease the initial dose of glargine by 20% to prevent hypoglycemia. Since it takes 2 – 4 days to reach steady levels, wait 3 days before increasing the dose.

What Injection Devices can be Used?⁴

Insulin glargine is available in a 10 mL vial for use with standard syringes. It is also available in 3ml cartridges that can only be used in insulin pen delivery systems such as the 'OptiPen Pro' or the disposable 'OptiSet' insulin pen, both from Aventis.

How should insulin glargine be administered?

It should be administered *once a day*, even if the previous insulin regimen was BID. It can be taken at any time of the day, but must be given at the same time each day: pre-breakfast, pre-lunch or at bedtime. Insulin glargine may be used either on its own or in combination with other insulins or oral anti-diabetic agents for optimal control. When switching to insulin glargine for intensive regimens, patients will still need short acting insulin to cover meals.⁴ The duration of action of insulin glargine is similar for abdominal, deltoid and thigh subcutaneous administration so patients can be advised that any of the above mentioned sites are appropriate.³

Are there any contraindications?⁴

Insulin glargine must not be diluted or mixed with any other insulin or solutions. If it appears to have any sediment it should not be used and must be discarded. Lantus is contraindicated in patients with hypersensitivity to insulin or its excipients (zinc, metacresol, glycerol, sterile water, HCl or NaOH for pH adjustment). Lantus should never be injected into a vein or muscle as this could lead to rapid hypoglycemia as its duration of action is dependent on subcutaneous administration.

Are there any interactions?⁶

Substances affecting glucose metabolism and making insulin dose adjustment and close blood glucose monitoring necessary.	
Drugs Increasing Hypoglycemic Activity	Alcohol, alpha-blockers, anabolic steroids, beta blockers (delay recovery, mask hypo), clofibrate, MAO inhibitors, guanethidine, pentamidine, phenylbutazone, salicylates, tetracyclines, sulfonamide antibiotics, fluoxetine, ACE-inhibitors, oral anti-diabetic drugs
Drugs Decreasing Hypoglycemic Activity	Corticosteroids, dextrothyroxine, diltiazem, dobutamine, epinephrine, niacin, OCP's, thiazide diuretics, thyroid hormone, smoking
Herbals	Chromium, garlic, and gymnema may increase the risk of hypoglycemia.

Precautions?

Pregnancy – Use cautiously in pregnancy as no studies have been done on the effects of insulin glargine in pregnant women.³ Due to the mitogenic potential, use in pregnancy is questionable.⁷

Lactation – Insulin is a large peptide not secreted into milk.⁸ Therefore it is safe to use while breastfeeding.

Renal and Hepatic Impairment – careful monitoring of blood glucose and dose adjustments is advisable due to study results showing increased levels of circulating insulin in these populations.⁴

Diabetic Ketoacidosis – Lantus is **NOT** the treatment of choice for diabetic ketoacidosis as it does not have a rapid enough onset of action. Intravenous short acting insulin is the preferred treatment.⁴

Mitogenic Potential - *In vitro*, insulin glargine increases both mitogenic potency and IGF-1 receptor affinity so, in theory, it could increase the chance of developing mammary, ovarian and bone tumors in addition to contributing to the development of diabetic retinopathy.⁷ However, no significant differences have been noted in studies comparing Lantus to NPH in regards to carcinogenicity.⁹ One small study did show that Lantus was associated with an increased incidence of retinopathy compared to NPH. This has prompted the FDA to mandate phase IV studies to see if this is the case.¹⁰

Have any adverse reactions occurred?⁶

Adverse reactions to insulin are very rare. Hypoglycemia is the most common adverse effect of insulin, including insulin glargine. Other reported adverse effects are similar in type and incidence to those occurring with other insulin formulations.

How does insulin glargine compare to NPH insulin?

	NPH Insulin	Insulin Glargine
Duration of action ⁴	14.5 hours	24 hours
Appearance ³	Cloudy	Clear
Safety/Efficacy based on race, gender, weight (obesity), age of patient ²	Comparable	Comparable
Adverse Events ^{1,2,4}	Comparable except: injection site pain 0.7%	Comparable except: injection site pain 2.7%
Hypoglycemia ^{1,2,11}	Similar - slightly more nighttime hypoglycemia, and blood sugars <2 mmol/L	Similar but studies indicate lower incidence of nocturnal hypoglycemia and FBG<2
Effectiveness in Type 1 and Type 2 DM ⁴	Comparable	May be slightly more effective at decreasing FBG and Hemoglobin A1C

How should Lantus[®] be stored?⁴

Unopened vials/cartridges: should be stored in the fridge (4 – 8° C), but care should be taken not to let it touch the freezer compartment. Discard if frozen.

Opened vials should be used within 28 days after the first use. They can be **refrigerated or un-refrigerated** if kept at < 30°C and away from direct light. Opened **cartridges** should **NOT** be kept in the fridge. They should be kept away from light and heat over 30°C and are usable for 28 days after opening.

Why haven't I seen Lantus[®] in practice?

Aventis Pharma received their notice of compliance (N.O.C.) from Health Canada on April 3, 2002. However, due to debate over the price, the product was not marketed in Canada until February 2005.¹² Lantus[®] is one of the most costly insulin therapies available. Wholesale cost for a 10mL vial is around \$57.82.¹³ It is far more expensive than NPH which costs \$17.20 per 10mL vial.¹⁴

Prepared by Krystal Hurlburt, SPEP student.

References are available by request or via the Internet on the Saskatchewan Drug Information Service website, www.usask.ca/druginfo, with the newsletter.

Suspect an adverse reaction?

REPORT IT -- FOR THE BENEFIT OF ALL!

Report forms are available in the CPS, on the Health Canada website (www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_adverse_e.html), or by request from the SaskAR Regional Centre.

Submit reports:

By telephone: 1-866-234-2345

By fax: 1-866-678-6789

By mail: Saskatchewan Regional Adverse Reaction Centre (SaskAR)

College of Pharmacy & Nutrition, University of Saskatchewan, 110 Science Place, Saskatoon SK S7N 5C9

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The Cochrane Library is considered the best single source of reliable evidence about the effectiveness of health care interventions. It is produced by the Cochrane Collaboration, an international non-profit and independent organization. The Library consists of seven different databases. The three most likely to be relevant for practicing pharmacists are:

1. The Cochrane Database of Systematic Reviews (CDSR)

A systematic review is a summary of the available evidence for and against the effectiveness and appropriateness of a specific treatment (drugs, education, etc.) for a specified medical condition in specific circumstances. To reduce the chance of bias, Cochrane Group reviewers follow strict protocols to ensure that literature searches are as comprehensive as possible. (Unpublished material may also be included.) Complete descriptions of reviews including references are provided.

2. The Database of Abstracts of Review of Effects (DARE)

This database contains abstracts of systematic reviews by the Cochrane Group and other researchers. The abstracts are written by the Centre for Reviews and Dissemination at the University of York in the United Kingdom, members of the Cochrane Heart Group and by members of the Oncology Expert Panel.

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CENTRAL is a list of healthcare articles from databases such as MEDLINE, EMBASE and other published and unpublished sources. It provides bibliographic information (title, source of article) and often a summary of the article. Full text of the article is not available.

Access to the Cochrane Library is available through local public libraries and regional health authorities.

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OR

- If you have a current public library card, log on to your local library website from your home or work computer. (Saskatchewan library websites are listed at www.lib.sk.ca).

OR

- If you work at a Saskatchewan regional health authority facility, log directly on to <http://www.thecochranelibrary.com> .

The Cochrane Library is a valuable, time-saving resource for pharmacists researching **patient-specific** questions. Check it out! If you have any problems accessing or using the Cochrane databases, call your local public librarian or the Saskatchewan Drug Information Service.

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