



Glargine (Lantus®): It's Place in Current Therapy

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Glargine (Lantus®) is a long-acting insulin that has received FDA approval in April 2000.¹ It is the first insulin that exhibits a so-called peak-less action.¹ The insulin used to make glargine is produced by *Escherichia coli* which is then further modified by recombinant technology. The structure of glargine is similar to human insulin, except that at the C-terminus of the B chain 2 arginines have been added and that asparagine has been exchanged for glycine at position A21.¹ These differences make glargine soluble at an acidic pH, but insoluble at a neutral pH.¹ Consequently, when glargine is injected subcutaneously microprecipitates in the shape of hexamers form which allow for a consistent, dose-dependent release of insulin, typically lasting 24 hours.¹ A number of studies have compared glargine to other basal insulins with promising results, such as a decreased risk for nocturnal hypoglycemia, improved glycemic control and enhanced quality of life.^{2,3,4,5,6}

Pharmacology and Pharmacokinetics:

Glargine is a long-acting insulin that mimics pancreatic basal insulin release as it is normally secreted from the beta-cells of the pancreas in patients without diabetes.^{1,7} Insulin is needed to stimulate insertion of Glut-4 transporters, primarily in adipose tissues and skeletal muscle cells, which allows uptake of glucose into the cell.⁸ Insulin promotes anabolism, such as lipogenesis and protein synthesis and inhibits catabolic processes, such as gluconeogenesis and lipolysis.^{1,7}

Glargine is administered subcutaneously and thus has 100% bioavailability. It has a slower onset of action than NPH insulin (3-4 hours versus 1-2 hours), however its duration of action is longer (24 hours versus 18 – 24 hours).⁹ The absorption of glargine is peak-less, decreasing the risk for hypoglycemia. NPH, on the other hand, has an unpredictable peak at 5-12 hours after injection.^{9,10} Glargine is metabolized into two active metabolites and many inactive metabolites.⁷ The effects of age, race, gender, smoking, pregnancy, renal failure and hepatic failure have not yet been adequately studied.⁷ Caution is advised when glargine is used in these special patient populations.^{1,7}

Indications and Dosing:

Glargine is FDA approved for pediatrics (> 6 years old) and adults with Type I diabetes mellitus (DM). It is also approved for adults with Type II DM who require long-acting basal insulin replacement.^{1,7} Glargine comes as a clear, colorless solution containing 100 Units/ml. The dose may be simply drawn out of the 10 ml vial via a syringe or may be purchased as a 3 ml cartridge named Opticlick®.¹¹ Glargine should only be used to replace basal insulin that is needed to control blood glucose between meals. It should

not be used as a substitute for bolus insulin which is needed to absorb glucose from meals. Dosing is patient specific and depends on many variables, including body mass and the cell's sensitivity to insulin. Glargine can be given at any time of the day, however once a time has been determined, it should be consistently taken around the same time. Glargine should be administered subcutaneously in either the abdomen, thigh or deltoid and should not be mixed with any other insulin nor be given intravenously (IV). Rotating of the site, but within the same area, is important to avoid lipodystrophy and potential changes in absorption. The following table is intended as a guide for initiation of insulin, 50% of the total insulin dose is to be used for basal insulin, while 50% is to be used for rapid or short-acting bolus insulin^{1,7}:

Safety:

Glargine is generally well tolerated. As with other insulins, hypoglycemia is the most common and serious adverse reaction reported. Other common side effects include Injection Site Reactions (ISR) which manifest as itching, rash or lipodystrophy. Due to the acidic pH of the solution, glargine tends to cause more pain upon injection than NPH. However, most ISRs are mild and temporary and have not led to an increased discontinuation rate in clinical trials.^{1,7}

The timed release formulation of glargine is dependent on the subcutaneous route. Direct IV administration causes immediate release of the entire insulin dose, potentially leading to severe hypoglycemia. Thus, the use of glargine by the IV route should be avoided. Rare cases of anaphylactic reactions have been reported that are possibly linked to antibody formation towards human insulin.^{1,7}

Clinical Trials:

Several trials have compared glargine with NPH, all showing either equal or even superior efficacy and safety of glargine. Chatterjee, et al² conducted a 36 week cross-over study with sixty type I DM patients in which he compared twice daily NPH with once daily glargine. Both study groups received aspart as their bolus insulin. Even though the study showed no difference in hypoglycemia and weight-gain, Fasting Plasma Glucose (FPG) was 3 mmol/L (55 mg/dL) (p=0.04) lower and glycosylated hemoglobin (HbA1c) was 0.19% lower (p=0.002) in the glargine group compared with the NPH group. Additionally, patients subjectively preferred glargine over NPH (p=0.001).

A meta-analysis of studies comparing glargine versus NPH con-

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ducted by Rosenstock, et al⁵ showed that even though HbA1c and FPG were similar in both groups, hypoglycemia occurred 11-62% (p= 0.0006-0.0461) less frequently in patients on glargine than on NPH insulin. This was especially true in the group with HbA1c < 7%. The authors concluded that tight insulin control might be more easily managed with glargine than NPH insulin due to the lower risk of hypoglycemia. This assumption was confirmed by Fulcher, et al¹² who conducted a 30 week study which compared NPH versus glargine given at bedtime. All patients received lispro which was given three times a day with meals to cover bolus insulin requirements. A total of 125 patients with Type I DM from 9 different centers participated in the study. The results showed a significant decrease in HbA1c (adjusted: 0.53% difference, p< 0.01), significant decrease in FPG (1.12 mmol/L (22 mg/dL); p< 0.05) and significant decrease in severe nocturnal hypoglycemia (28 people in the glargine group versus 41 in the NPH group; p<0.02). Even though glargine has not been officially studied in the United States (US) regarding its cost-effectiveness, both the United Kingdom (UK) and Canada have conducted such studies to determine whether glargine is worth its expense^{4,6}. McEwan, et al⁶ estimated the cost per Quality Of Life Year (QOLY) for a patient with Type I DM to be between £ 3189 - £ 9767. This is well below the £ 20,000 which the UK National Health Service (NHS) uses as their cut-off to determine cost-effectiveness. Grima, et al⁴, also determined that glargine is cost-effective for Type I and Type II DM patients in Canada. Patients on glargine had an incremental life-year gain of 0.52-0.59 in Type II DM patients and 0.21-0.24 in Type I DM patients leading to an incremental cost of \$ 8041 for Type II DM and \$ 18,661 for Type I DM. Average incremental Quality Adjusted Life Years (QALY) gained was 0.231 for Type II DM and 0.067 for Type I DM which resulted in an incremental cost of \$ 8618 for Type II DM and \$ 20,799 for Type I DM. Despite the fact that these results cannot be extrapolated, it is the authors opinion that the use of glargine is highly likely to be cost-effective in the US, as well.

Summary:

Glargine is a new long-acting insulin that provides an added advantage to current therapy due to its peak-less action. The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have clearly shown that tight insulin control improves outcomes in patients with Type I and Type II DM.^{13,14} Nonetheless, tight insulin control brings along an increased risk of hypoglycemia.¹⁵ It also requires strong patient motivation and adherence to the drug therapy prescribed. Glargine with its peak-less action and convenient once-a-day dosing regimen makes it easier for patients to control their blood glucose and thus live a healthy life. Despite the fact that glargine has a higher acquisition cost, the increased quality and length of life patients seem to experience with this drug, makes glargine a cost-effective alternative to other basal insulins in patients with Type I and II DM.

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Table 1:

	Type I DM	Type II DM
Initial dose (weight based)	0.5—0.6 units/kg/day	0.2—0.6 units/kg/day
Initial dose (standard dose, based on glargine alone – does not include bolus insulin)	n/a	10 units (if insulin naïve, but recently treated with oral hypoglycemics), followed by 2-100 units
Initial dose when switching from NPH	Decrease previous NPH dose by 20%	Decrease previous NPH dose by 20%
Dosing schedule for NPH	Bid	Daily (bedtime), followed by bid dosing
Dosing schedule for Lantus	Daily	Daily

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Table 2

Indication	Basal insulin replacement in Type I DM (≥ 6 years old) and Type II DM (≥ 18 years old)										
Dosing	<p><i>Initial dose:</i> 0.5-0.6 units/kg/day (Type I) or 0.2-0.6 units/kg/day (Type II)</p> <p>OR 10 units in Type II DM patients, who have previously been on oral hypoglycemics</p> <p><i>Max dose:</i> Based on patients response and individualized blood glucose target</p>										
PK	<table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left; border-bottom: 1px solid black;"><u>Onset</u></th> <th style="text-align: left; border-bottom: 1px solid black;"><u>Peak</u></th> <th style="text-align: left; border-bottom: 1px solid black;"><u>Duration</u></th> <th style="text-align: left; border-bottom: 1px solid black;"><u>Metabolism</u></th> <th style="text-align: left; border-bottom: 1px solid black;"><u>Excretion</u></th> </tr> </thead> <tbody> <tr> <td>3-4 hours</td> <td>n/a</td> <td>24 hours</td> <td>2 active m/b</td> <td>urine</td> </tr> </tbody> </table>	<u>Onset</u>	<u>Peak</u>	<u>Duration</u>	<u>Metabolism</u>	<u>Excretion</u>	3-4 hours	n/a	24 hours	2 active m/b	urine
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3-4 hours	n/a	24 hours	2 active m/b	urine							
Precautions	Do not use via IV route due to the potential for severe hypoglycemia										
Adverse Events	<p>Most common and severe: hypoglycemia (possibly less than other insulins)</p> <p>Common: Injection Site Reactions (e.g. rash, itching, lipodystrophy)</p> <p>Rare: anaphylactic reaction</p>										
Dosage Forms	<p>Lantus Solution for Injection (100 Units/mL)</p> <ul style="list-style-type: none"> - 10 ml vial - Opticlick® 3 ml vial cartridge (in packages of 5) 										

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