

NEW DRUG UPDATE

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Lantus® (insulin glargine)

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Introduction:

Lantus® (insulin glargine [rDNA origin] injection) {IN-su-lin g-LAR-geen} is a long-acting recombinant insulin analog that was FDA approved in April 2000 for the treatment of types 1 and 2 diabetes. Insulin glargine is the first long-acting recombinant human insulin analog that is indicated for once-daily subcutaneous administration at bedtime in the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal insulin for the control of hyperglycemia.

Therapeutic Recommendation:

CONTROLLED CLINICAL TRIALS HAVE SHOWN THAT INSULIN GLARGINE IS MORE EFFECTIVE WHEN COMPARED TO NPH HUMAN INSULIN AT IMPROVING GLYCEMIC CONTROL IN PATIENTS WITH TYPE 1 DIABETES. CLINICAL TRIALS HAVE ALSO REPORTED THAT INSULIN GLARGINE DECREASES HGBA_{1C} AND/OR FASTING BLOOD GLUCOSE LEVELS TO A SIMILAR EXTENT AS THAT SEEN WITH NPH INSULIN IN TYPE 2 DIABETICS. DUE TO THE FORMULATION OF LANTUS®, A CONSTANT RELEASE OF INSULIN PROVIDES A SLOW ABSORPTION WITH NO PRONOUNCED PEAK AND A GLUCOSE LOWERING EFFECT OF OVER 24 HOURS. THE ONCE DAILY DOSING AND POTENTIAL TO CAUSE LESS HYPOGLYCEMIA THAN NPH INSULIN APPEAR FAVORABLE FOR INSULIN

GLARGINE AS AN AGENT TO SATISFY THE BASAL INSULIN REQUIREMENTS FOR BOTH TYPE 1 AND TYPE 2 DIABETES MELLITUS PATIENTS. THE RELATIVELY HIGHER COST OF INSULIN GLARGINE MAY ALSO BE A FACTOR FOR CONSIDERATION WHEN PRESCRIBING.

Dosing and Administration:

Lantus® (insulin glargine) is supplied in 5 ml vials, 10 ml vials, and 3 ml cartridges (packages of 5). All preparations contain 100 units/ml insulin glargine. The 3 ml cartridges are for use in the Opti-Pen® One insulin delivery device.

Cost Comparison:

| Medication/Dose | Cost** | | |
|---|----------|----------|--------|
| | Rite Aid | Wal-Mart | K-Mart |
| Lantus® (insulin glargine) | 59.99 | 48.46 | 50.00 |
| Humulin N® (isophane insulin suspension, NPH) | 25.98 | 24.10 | 21.39 |
| Novolin N® (isophane insulin suspension) | 25.38 | 16.94 | 20.99 |
| Humulin L® (insulin zinc suspension, lente) | 24.68 | 21.70 | 21.39 |
| Novolin L® (insulin zinc suspension, lente) | 24.68 | 16.84 | 19.99 |

*Cost to patient for a 10 ml vial. Note: Usual 30 day supply may vary. When analyzing cost, consider QD vs. BID dosing.

Inside This Issue:

- ▶ Lantus® (Insulin glargine)
- ▶ Welchol® (Colesevelam HCl)

Insulin glargine must not be diluted or mixed with any other insulin or solution, as it may result in a delayed onset of action. Insulin glargine should be administered subcutaneously once daily at bedtime. The desired blood glucose levels as well as the doses and timing of insulin glargine must be determined individually. In a clinical study of patients with type 2 diabetes not currently receiving insulin therapy, but who were receiving oral antidiabetic drugs, insulin glargine was started at an average dose of 10 IU once daily. Doses were then subsequently adjusted according to the patients need to a total daily dose ranging from 2 to 100 IU per day. In clinical studies, when patients were transferred from once-daily NPH human insulin or ultralente human insulin to once-daily insulin glargine, the initial dose was not changed. However, when patients were changed from twice-daily NPH human insulin to insulin glargine once daily at bedtime, to reduce the risk of hypoglycemia, the initial dose of insulin glargine was reduced by approximately 20% within the first week of treatment and then adjusted based on individual patient response.

Insulin glargine can be safely administered to pediatric patients 6 years or older. Dosage recommendations for changeover to insulin glargine are the same as for adults.

Insulin glargine can be administered subcutaneously in the abdomen, thigh or deltoid. As with all insulin, injection sites must be rotated from one injection to the next. The rate of absorption, and the onset of action may also be affected by exercise and other variables.

Warnings / Precautions:

Insulin glargine is not indicated for administration by the intravenous route. Intravenous administration of the usually subcutaneous dose could result in severe hypoglycemia. Insulin glargine must not be diluted or mixed with other insulin or solutions. If insulin glargine is mixed or diluted it could result in an altered and unpredictable pharmacokinetic/ pharmacodynamic profile. As with all insulin products, insulin glargine may have inter patient variability, as the rate of absorption is dependent on blood supply, temperature, and physical activity. Hypoglycemia is the most common adverse effect of insulin, including insulin glargine. The prolonged effect of subcutaneous insulin glargine may delay recovery from hypoglycemia. Glucose monitoring is strongly recommended in all patients with diabetes.

Contraindications:

Insulin glargine is contraindicated in patients with hypersensitivity to insulin glargine or the excipients contained in its formulation.

Special populations:

Renal impairment: Studies have not been performed using insulin glargine in patients with diabetes and renal failure; however, insulin glargine requirements may be diminished because of reduced insulin metabolism, which has been observed with other insulin products. Careful glucose monitoring and dose adjustments of insulin glargine may be necessary in patients with renal dysfunction.

Hepatic impairment: Studies have not been performed using insulin glargine in patients with diabetes and hepatic impairment; however, insulin glargine requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism, which has been observed with other insulins. Careful glucose monitoring and dose adjustments of insulin glargine may be necessary in patients with hepatic dysfunction.

Pregnancy: Pregnancy category C. There are no well-controlled clinical studies of insulin glargine used in pregnant women at this time. This drug should be used during pregnancy only if clearly needed.



...A Primary Care Physician's Guide to Newly Released Medications...

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Lactation: It is unknown whether insulin glargine is excreted in human milk in appreciable amounts; therefore, caution should be exercised when administering insulin glargine to a nursing mother.

Pediatric use: Insulin glargine has been established as safe and effective in children age 6 to 15 with type 1 diabetes.

Geriatric use: The initial dose, dose increments, and maintenance dose of insulin glargine, as with other insulin products used in elderly patients should be conservative to avoid hypoglycemic reactions, which may be difficult to recognize in this subpopulation of patients

Intercurrent conditions: The dosage of insulin glargine, as with other insulins may need to be adjusted during intercurrent conditions such as, illness, emotional disturbances, or stress.

Drug Interactions:

Many substances may increase or lower blood-glucose levels requiring insulin dose adjustment and careful monitoring.

Substances known to increase the blood-glucose lowering effect and lead to hypoglycemia: oral antidiabetic products, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide) sulfonamide antibiotics.

Substances known to reduce the blood-glucose lowering effect of insulin: corticosteroids, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), isoniazid, phenothiazine, derivatives, somatropin, thyroid hormones, estrogens, progestins.

Substances that may either increase or reduce the blood-glucose effects of insulin: beta-blockers, clonidine, lithium salts, and alcohol. Pentamide may cause hypoglycemia, which may be followed by hyperglycemia.

Beta-blockers, clonidine, guanethidine, and reserpine have the potential to reduce or mask the signs of hypoglycemia.

Common Adverse Effects:

Insulin glargine has been well tolerated in large clinical trials as well as in several smaller trials with an adverse event profile similar to that of NPH insulin. Adverse events associated with insulin glargine include the following:

Hypoglycemia: The most common adverse effect of insulin, including insulin glargine is hypoglycemia. In one study including 333 patients the frequency of nocturnal hypoglycemia was significantly lower in insulin glargine recipients than in NPH insulin recipients (36% with insulin glargine vs 55% with NPH insulin, $p = 0.0037$). However, the overall frequency of hypoglycemia did not differ between the two groups.

Skin and appendages: Lipodystrophy, as associated with other insulins, may occur at the injection site and delay the absorption of insulin glargine. Other injection site reactions may include redness, pain, itching, hives, and swelling. These may be reduced or prevented by rotating the injection site each time that insulin is administered. In clinical studies insulin glargine was associated with a higher rate of treatment-emergent injection-site pain (2.7% in insulin glargine recipients vs 0.7% in NPH insulin recipients.)

Allergic Reactions: Reactions to insulin or the excipients are rare. Hypersensitivity to insulin or the excipients may be associated with generalized skin reactions, angioedema, bronchospasm, hypotension, or shock and may be life threatening.

Pharmacology:

Mechanism of Action: The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogs lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

Absorption/Distribution: Clinical trials have shown that insulin glargine has a relatively constant therapeutic effect with no pronounced peak. Insulin glargine is designed to have low solubility properties at neutral pH. At an acidic pH of 4, as in the insulin glargine injection solution, it is completely soluble. Once insulin glargine is injected into the subcutaneous tissue, the acidic solution is neutralized, leading to the formation of microprecipitates. These microprecipitates release small amount of insulin glargine slowly, resulting in a constant concentration/time profile over 24 hours. The longer duration of action is directly related to its slow rate of absorption. As with other insulins, the pharmacodynamics with insulin glargine may vary between individuals, and sometimes variances may be seen within the same patient.

Metabolism/Elimination: Insulin glargine is partly metabolized in the subcutaneous depot to form two active metabolites [M1 (21^A-Gly-insulin) and M2 (21^A-Gly-des-30^B-Thr-insulin) with *in vitro* activity similar to that of insulin. Unchanged drug, M1 and M2 are also present in the circulation. Information regarding elimination of insulin glargine is not available at this time.

Patient Information:

1. Insulin glargine should only be used if the solution is clear and colorless with no particles visible.
2. Insulin glargine must not be diluted or mixed with any other insulin or solution.
3. Self-blood glucose monitoring is recommended for all patients with diabetes.
4. Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy.
5. Illness may affect the amount of insulin you need. Check your blood sugar often and call your health care provider if you are sick.
6. Other medicines can change the way your insulin works. Be sure to tell your physician and pharmacist all other medications you are taking.
7. Exercise may change the way your body uses insulin. Be sure to check with your physician before starting an exercise program.
8. Store new insulin glargine vials in the refrigerator between 36°F – 46°F (2°C – 8°C). Do not freeze. If a vial freezes, throw it away. Once a vial is opened, you should keep it in the refrigerator or as cool as possible. The 10mL vial is good for 28 days once opened. The 5 mL vial is good for 14 days once opened if stored in a cool place (below 86°F [30°C]) or 28 days if refrigerated. Keep insulin glargine out of direct heat and light.

9. If using OptiPen®One, once a cartridge is placed in the pen, it should not be refrigerated.

References:

1. Gillies PS; Figgitt DP; Lamb HM. Insulin glargine. *Drugs* 2000 Feb;59(2):253-60.
2. Lantus® (insulin glargine [rDNA origin] injection) prescribing information. Aventis Pharmaceuticals Inc. Kansas City, MO, April 2000.
3. Heinemann L; Linkeschova R; Rave K; Hompesch B; Sedlak M; Heise T. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. *Diabetes Care* 2000 May;23(5):644-9.
4. AHFS *firstFAX* new drug overview: insulin glargine. *Am J Health-Syst Pharm.* Vol 57 Nov 1, 2000:1961.

Welchol® (colesevelam hydrochloride)

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Introduction:

Welchol® (colesevelam hydrochloride, (koe le sev' e lam) is a new lipid lowering agent that was FDA approved in June 2000. Colesevelam is a bile acid binder that is administered alone or in combination with an HMG-CoA reductase inhibitor that is indicated for the reduction of elevated low-density lipoprotein cholesterol in patients with primary hypercholesterolemia, as an adjunct to diet and exercise.

Therapeutic Recommendation:

COLESEVELAM IS AN EFFECTIVE LIPID LOWERING AGENT AND IS SIMILAR IN EFFECT TO OTHER BILE ACID SEQUESTRANTS (BAS) SUCH AS CHOLESTYRAMINE. ALTHOUGH THESE OLDER DRUGS HAVE PROVEN EFFICACY AND LACK SYSTEMIC SIDE EFFECTS CAUSED BY NONABSORPTION IN THE GASTROINTESTINAL TRACT, A HIGH DISCONTINUANCE RATE IS SEEN PARTIALLY DUE TO GASTROINTESTINAL (GI) SIDE EFFECTS SUCH AS CONSTIPATION, WHICH OCCURS IN UP TO 10-39% OF PATIENTS. OTHER GI SIDE EFFECTS SUCH AS BLOATING, FLATULENCE, AND CRAMPING HAVE ALSO

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OCCURRED IN A LARGE PERCENTAGE OF PATIENTS ON OLDER BAS. COLESEVELAM IS A NON-ABSORBED LIPID-LOWERING POLYMER THAT IS NOT HYDROLYZED BY DIGESTIVE ENZYMES, THUS REDUCING THE POTENTIAL FOR ADVERSE SIDE EFFECTS. ITS WATER-RETAINING ABILITY CREATES A SOFT, GELATINOUS MATERIAL THAT MINIMIZES GI IRRITATION. BAS MAY BE USED AS INITIAL CHOLESTEROL-LOWERING THERAPY AND ARE GENERALLY REGARDED SAFER THAN ABSORBED AGENTS SUCH AS NIACIN, FIBRATES OR HMG CO-A REDUCTASE INHIBITORS (HRIs) WHICH REQUIRE FREQUENT LIVER FUNCTION TESTS, AND MAY CAUSE MYALGIAS.

SEVERAL CONTROLLED TRIALS HAVE SHOWN THAT COLESEVELAM CAN DECREASE LDL BY 15-18% AND DECREASE TOTAL CHOLESTEROL BY 7-10%. THE MAXIMAL THERAPEUTIC EFFECT WAS FOUND AT 2 WEEKS AND WAS MAINTAINED THROUGHOUT A 6-WEEK STUDY PERIOD. SMALL INCREASES IN TRIGLYCERIDES WERE DETECTED, BUT WERE NO DIFFERENT THAN PLACEBO. WHEN COLESEVELAM WAS GIVEN IN COMBINATION WITH ATORVASTATIN OR SIMVASTATIN, THE TOTAL REDUCTION IN LDL WAS SUPERIOR TO THAT ACHIEVED WITH COLESEVELAM OR THE SAME DOSE OF THE HRI ALONE. COLESEVALAM OFFERS THE ADVANTAGE OF A TABLET FORM WITH LESS MESS VERSUS THE OLDER BAS IN POWDER FORMULATION. HOWEVER, THIS CAN CREATE A LARGE TABLET BURDEN FOR PATIENTS WHO MUST TAKE 3-7 TABLETS AT ONE TIME. THE COST OF COLESEVELAM SEEMS TO BE SUBSTANTIALLY HIGHER THAN THE TRADITIONAL BAS AS WELL AS THE HRIs. THE LOWER INCIDENCE OF GI SIDE EFFECTS IN COMPARISON WITH THE OLDER BAS AND NO INDICATIONS FOR LIVER FUNCTION TESTS OR MYALGIA AS WITH HRIs HELP DEFINE COLESEVELAM'S ROLE IN HYPERLIPIDEMIA.

Dosing and Administration:

Welchol® is available in 625 mg tablets that are off-white, solid and imprinted with the word "Sankyo" over "C01". The starting dose for monotherapy is 3 tablets taken twice per day with meals or 6 tablets once per day with a meal. This dose can be increased to 7 tablets depending on the target effect. The starting dose for combination therapy with an HMG-CoA reductase inhibitor is colesevelam 3 tablets taken twice per day with meals or 6 tablets taken once daily with a meal. Colesevelam should be taken with at least 4 oz of liquid.

Cost Comparison:

| Medication/Dose | Cost** | | |
|---------------------------|-----------------|-----------------|--------------|
| | <u>Wal-Mart</u> | <u>Rite Aid</u> | <u>Fruth</u> |
| Questran (Cholestyramine) | \$95.68 | \$76.22 | \$70.00 |
| Colestid (Colestipol) | 140.00 | * | * |
| Welchol (Colesevelam HCl) | 198.54 | 189.69 | 146.48 |

**Cost to patient for a 30-day supply at average doses used.

* Not available

(generic)

Warnings / Precautions:

General: Caution should be exercised when treating patients with triglyceride levels greater than 300mg/dl because colesevelam has the potential to increase triglycerides.

Caution should be exercised when treating patients with a susceptibility to vitamin K or fat-soluble vitamin deficiencies because colesevelam may interfere with the absorption of fat-soluble vitamins.

Caution should be exercised when colesevelam is used in patients with dysphagia, swallowing disorders, severe gastrointestinal motility disorders, or major gastrointestinal tract surgery due to large tablet size.

Contraindications:

Colesevelam is contraindicated in patients with bowel obstruction and in individuals who have shown hypersensitivity to any of the components of colesevelam.

Special populations:

Pregnancy: Category B. Reproduction studies have been performed in rats and rabbits and have revealed no evidence of harm to the fetus due to colesevelam, but there are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed.

Pediatric Use: The safety and efficacy of colesevelam have not been established in pediatric patients.

Geriatric Use: There is no evidence for special considerations when administered to elderly patients.

Hepatic impairment: No dosage adjustment is necessary in patients with hepatic compromise.

Renal impairment: No dosage adjustment is necessary in patients with renal impairment.

Drug - Drug Interactions:

Colesevelam was found to have no significant effect on the bioavailability of digoxin, lovastatin, metoprolol, quinidine, valproic acid, and warfarin. Colesevelam decreased the C_{max} and AUC of sustained-release verapamil (Calan SR) but the clinical significance of this finding is unclear. Co-administration of colesevelam with atorvastatin, lovastatin, or simvastatin did not interfere with the lipid-lowering activity of the HMG-CoA reductase inhibitor. Other drugs have not been studied for interactions with colesevelam, although it may be recommended to space doses of other drugs 1 hour before or 4 hours after taking colesevelam due to the potential for decreased absorption.

Common Adverse Drug Reactions:

In placebo-controlled trials involving approximately 1065 patients, adverse events (occurring at a rate of >2%) that occurred more frequently with colesevelam treatment compared with placebo, included asthenia (4% vs. 2% placebo), constipation (11% vs. 7% placebo), dyspepsia (8% vs. 3% placebo), and myalgia (2% vs. 0% placebo).

Pharmacology:

Mechanism of Action: Cholesterol is the sole precursor of bile acids, which are made by the liver and sent to the intestines to help digest fats. Bile acid sequestrants such as colesevelam, bind to bile acids in the in-

testine and impede their reabsorption. To replenish the bile acid pool, the liver draws cholesterol from the bloodstream, resulting in lower blood cholesterol levels.

Absorption/Distribution: Colesevelam is not hydrolyzed by digestive enzymes and is not absorbed.

Metabolism/Elimination: An average of 0.05% of a single carbon 14 labeled colesevelam dose was excreted in the urine when given following 28 days of chronic dosing of 1.9 grams of colesevelam twice per day. The rest of the colesevelam binds with the bile acids and is eventually excreted in the stool.

Patient Information:

- 1) Colesevelam may be taken once per day with a meal, or taken twice per day in divided doses with meals.
- 2) Take with at least 4 oz of liquid and a meal. Adhere to recommended low-cholesterol diet.
- 3) Tell your physicians if you are pregnant, intending to become pregnant, or are breast-feeding
- 4) Consider spacing medication 1 hour before or 4 hours after taking colesevelam to increase absorption.
- 5) You may need to increase fiber and liquid consumption to prevent or decrease constipation.

References:

- 1) WelChol® prescribing information. GelTex Pharmaceuticals, Inc., June 2000.
- 2) Davidson, Michael H. et al. Colesevelam Hydrochloride (Cholestagen). Archives Internal Medicine 1999;159: 1893-1900
- 3) http://pharminfo.com/pubs/druginfoline/druginfo2_72c.html



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