Emerging Drug List
INSULIN GLARGINE

CANADIAN COORDINATING OFFICE FOR HEALTH TECHNOLOGY ASSESSMENT

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Generic (Trade Name): Insulin glargine [rDNA origin] (Lantus®)

Manufacturer: Aventis Pharma Inc.

Indication: For the treatment of both adults and children (six years of age and older) with type 1 diabetes mellitus or adults with type 2 diabetes mellitus that require hyperglycemia control with a long-acting insulin.

Current Regulatory Status: The European Agency for the Evaluation of Medicinal Products approved insulin glargine in June 2000. In the United States, insulin glargine was approved for marketing in April 2000, with an expected marketing date in the summer of 2001. According to prescribing information, it will be marketed as a 100 u/ml solution in 5 ml and 10 ml vials, along with 3 ml cartridges that are used with the OptiPen® One Insulin Delivery Device. Information regarding the release date in Canada is currently unavailable.

Description: Insulin glargine is a long-acting human insulin prepared using recombinant DNA technology. The chemical structure has been modified to include glycine at position A21, rather than asparagine, along with the addition of two arginines on the beta chains at the C-terminus position. The product itself is an acidic (pH 4) solution, but upon injection into the subcutaneous tissue is neutralized. This process creates microprecipitates that release small amounts of insulin over a 24-hour period. This formulation allows for a more consistent release of insulin over the day, without pronounced peaks, thereby mimicking natural basal insulin release. The product is typically administered at bedtime. There are dosing recommendations within the prescribing information when transferring a patient from other insulins. As with other long-acting insulins, it is not to be administered intravenously. Some differences from other long-acting products are that is it colorless, it does not require re-suspension (shaking) prior to drawing up the dose, and it cannot be mixed with other insulin products (e.g., regular insulin).

Current Treatment: In Canada, there are various human insulin formulations available as very rapid, intermediate and long-acting agents. These products include insulin lispro (Humalog®), insulin regular (Humulin® R, Novolin®ge Toronto), insulin lente/insulin NPH (Humulin® N, Humulin® L, Novolin®ge NPH, Novolin®ge Lente), and insulin ultralente (Humulin® U, Novolin® Ultralente). For ease of use, there are also premixed agents available (e.g., Humalog® Mix25™, Humulin® 30/70, Novolin®ge 30/70).

Cost: The cost of this product was unavailable at the time of this review.

Evidence: Rosenstock and colleagues conducted a 28-week, randomized, multicentre, open-label trial assessing the efficacy and safety of insulin glargine as compared to NPH insulin. Patients, aged 40 to 80 years, with type 2 diabetes received either insulin glargine once daily at bedtime (n=259) or NPH once or twice daily (n=211, 48 respectively). The doses were individually adjusted to a target fasting glucose value of <6.7mmol/L. Regular pre-meal insulin was continued as necessary. Efficacy endpoints included a change in HbA1c, fasting blood glucose (FBG), and adverse effect profile.

At week 28, the median total daily dose of insulin was comparable between the groups at 0.75IU/kg. Both groups had a statistically significant difference in HbA1c from baseline (p=0.0001) however, this difference was not noted between the treatment groups. Similarly, the percentage of patients that achieved the target FBG was similar between treatment groups at 29.6% and 27.1% for insulin glargine and NPH, respectively. Symptomatic hypoglycemia was reported in both groups throughout the study, at 61.4 % and 66.8 % for insulin glargine and NPH, respectively. Reports of nocturnal hypoglycemia were more frequent throughout the trial in the NPH group, by 31.3% versus 40.2% of patients (p=0.0160). Excluding the

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Evidence (cont'd):

dose titration phase, 26.6% and 35.5% of insulin glargine and NPH subjects, respectively, reported one or more episodes of nocturnal hypoglycemia (p=0.0136).

Yki-Järvinen et al examined the efficacy and safety of insulin glargine, as compared to NPH insulin, in adult type 2 diabetics during a 52-week trial. Patients (n=426) received either a bedtime dose of insulin glargine or NPH, and oral antidiabetic medications were continued. The insulin dose was titrated to obtain a FBG target of # 6.7 mmol/L. Efficacy endpoints included HbA1c, blood glucose profile and the incidence of hypoglycemia. At the end of the study, the insulin doses were comparable between the treatment groups. Changes in HbA1c from baseline were significant in both groups ($p < 0.001$) however, were not statistically different between treatment groups. In patients who reached the FBG target, overall there were less episodes of symptomatic hypoglycemia in the insulin glargine group (33% vs 50.7%, p=0.027). Nocturnal hypoglycemia was similarly lower in the insulin glargine group than the NPH group, for those that didn't meet the FBG target (9.0% vs 21.4%, p=0.012) and for those who did (12.6% vs 28.8%, p=0.011).

Adverse Effects:

Adverse effects associated with the use of insulin glargine include hypoglycemia, injection site reactions, pain at the injection site (2.7%), rash, and pruritis. Concerns regarding ocular safety arose secondary to an observation in one study showing a three-grade progression of retinopathy in some patients who received insulin glargine. However, upon review of the data, an independent panel did not determine that this effect was drug-related. The company will be examining this parameter further in a phase IV study, expected to end in October, 2004.

Conclusion:

Diabetes mellitus is a common disease associated with both microvascular and macrovascular complications. It currently affects over two million Canadians, and accounts for approximately nine billion dollars annually in health-care spending on the disease itself and its complications. Insulin glargine is expected to be advantageous secondary to its pharmacokinetic profile, allowing for a smoother release/concentration over a 24-hour time frame, thereby more closely mimicking basal insulin secretion. It appears to be comparable to NPH insulin in terms of its effect on HbA1c, an index of glycemic control. However, as it cannot be administered in combination with other agents, some patients may need to inject themselves more frequently, a situation that may not be desirable to all.

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The contents of this bulletin are current as of May 24, 2001

The **Emerging Drug List** highlights drugs not yet approved in Canada that are anticipated to have a significant impact on the health care system. Minimal information is available about these drugs, and they may, in the future, become the subject of an early assessment.

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