



## Executive Summary

### DIABETES MELLITUS AND GLUCOSE CONTROL

Diabetes is widely acknowledged as an immense and growing public health problem. The disease is associated with increased risk of death, decreased quality of life and costly, dangerous complications. At the root of these problems is the loss of the body's natural ability to produce and use insulin to maintain normal levels of glucose in the blood.

For many patients with diabetes, one of the central means of maintaining blood glucose control is through the external delivery of insulin. For a patient whose body produces little or no insulin, external insulin delivery must simulate two types of internal insulin secretion: a bolus secretion, which is a rapid-onset, high-level secretion of insulin in response to meals, and a basal secretion, which provides a constant, low-level of insulin for the body's between-meal metabolic demands. By delivering insulin at the right time and in the right amount, patients can keep their blood glucose at near normal levels, which will limit the development of serious, long-term complications such as blindness, kidney failure and limb amputation,<sup>1</sup> and subsequently decrease risk of death and increase quality of life.

### BIOTECHNOLOGY INNOVATION IN DIABETES: INSULIN ANALOGS

#### Advances in Insulin Therapy

One of the most significant areas of recent innovation in diabetes treatment has been the development of new forms of insulin, called insulin analogs, which allow the body to more closely mimic the natural regulation of blood glucose that occurs in people without diabetes. Insulin analogs promise improvements in blood glucose control by decreasing the frequency of hypoglycemic (low blood sugar) events and reducing hemoglobin A1C<sup>1</sup> levels. A1C levels are an established proxy for average blood glucose level over time and a strong indicator of long-term complication development. Insulin analogs are also more convenient for patients to take than regular insulin and thus have the potential to improve patient compliance with treatment regimens.

This report analyzes two classes of insulin analogs: rapid-acting insulin analogs and long-acting insulin analogs. Rather than examining the differences among specific products within each class, this analysis focuses on the benefits of each class of insulin analog as a whole:

- Rapid-acting insulin analogs, such as lispro, aspart and glulisine, take effect and lose effect faster than regular insulin (RI), which helps patients

---

<sup>1</sup> The A1C test measures the percentage of glycated hemoglobin (hemoglobin with glucose bonded to it) in the blood, which in turn corresponds to a patient's average blood glucose over a period of two to three months. An A1C level between 4 percent and 6 percent is considered typical for people without diabetes.



control the rapid change in glucose levels (bolus) that accompanies a meal.

- Long-acting insulin analogs, such as glargine and detemir, improve upon Neutral Protamine Hormone (NPH) by providing the more constant, low-level of insulin (basal) that the body needs between meals.

Insulin analogs can be incorporated into a patient's treatment regimen in a variety of different ways, depending on factors such as the stage of a patient's disease, lifestyle considerations, and the specific times when the patient's blood glucose reaches abnormal levels. For patients who require only bolus or basal insulin, analogs can often replace the patient's traditional insulin. For patients who require both bolus and basal therapy (known as insulin replacement), analogs have been used in two ways. *Independent use* describes the use of a rapid-acting analog to replace RI as the bolus insulin, while maintaining NPH as a basal insulin, **or** the use of a long-acting analog to replace NPH as a basal insulin, while maintaining RI as a bolus insulin. Recently, studies have also explored the use of rapid- and long-acting analogs in *combination use*—a regimen of rapid-acting **and** long-acting insulin replacing a regimen of RI and NPH.<sup>2</sup>

### Benefits

In general, the use of rapid- and long-acting insulin analogs is expected to have major benefits in two critical areas of diabetes treatment:

- **Blood Glucose Control:** Landmark clinical trials have shown that intensively managing blood glucose levels to remain within a near-normal range can dramatically decrease the risk of some long-term complications associated with diabetes. Insulin analogs provide benefits in intensive insulin therapy by:
  - Reducing the variability of blood glucose levels over time. When used as independent agents, both rapid- and long-acting analogs have generally been found to be as effective as traditional insulins in controlling blood glucose levels (represented by a reduction in A1C levels). A recent study has also shown that insulin analogs can provide an even greater reduction in A1C than a regimen of traditional insulins when the analogs are used in combination.<sup>2</sup>
  - Reducing the frequency of hypoglycemia. Clinical trials of rapid- and long-acting insulin as independent treatments, and in combination therapy, showed that treatment with analogs generally yields lower rates of hypoglycemia than treatment with traditional insulin.<sup>3</sup>
- **Patient Convenience:** Patient convenience is critical to the self-management of diabetes, as it greatly impacts patients' decisions about how aggressively to manage their conditions. Therefore, the convenience



factor and short-term quality of life improvements will ultimately drive improved health outcomes. Insulin analogs:

- Increase patients' comfort with pursuing tight control of blood glucose by reducing the frequency of hypoglycemia.
- Ease the burden of insulin delivery on patients by allowing them to take rapid-acting insulin with a meal (or in some cases within 20 minutes after starting a meal), rather than 30 to 60 minutes before eating.
- Reduce the number of injections of long-acting insulin, depending on the specific treatment regimen.

### Value

This progress in the treatment of diabetes could not be timelier. As innovations, like insulin analogs, deliver better care to patients, it becomes increasingly important to examine the benefits of these innovations relative to their costs. In today's cost-conscious health care environment, there is a growing movement to assess innovations based on value—that is, to determine the benefit of an innovation relative to its cost—rather than to evaluate it on product acquisition cost alone.

In this analysis, NEHI has taken two approaches to examining the value of insulin analogs:

- A traditional cost-effectiveness approach (cost-utility analysis)<sup>4</sup> to determine the value of insulin analog drugs used in combination therapy. Extrapolation of results from the largest randomized trial of combination use in type 1<sup>ii</sup> patients demonstrates that insulin analogs are indeed cost-effective.
- A qualitative review of the benefits of insulin analogs to determine whether increased convenience of drug administration improves the management of diabetes. Patient and clinician experiences suggest that insulin analogs have significant convenience and quality of life benefits that are critical to the long-term management of diabetes. However, these benefits are not quantified fully in NEHI's value analysis because they have not yet been adequately measured in the literature.

### *Cost Effectiveness*

Insulin analogs can be used in a variety of different treatment regimens depending on the stage and type of a patient's disease. A cost-effectiveness evaluation for

---

<sup>ii</sup> In type 1 diabetes, the pancreas is unable to produce insulin and patients must inject or infuse external insulin in order to live.



each use is beyond the scope of this report.<sup>5</sup> Instead, NEHI's cost-effectiveness analysis examines the specific case of combination insulin analog therapy in type 1 patients. This analysis serves as a case study of the value that insulin analogs can provide. Evaluating the costs and benefits of combination insulin analog therapy in type 1 patients does appear to be cost effective, with a base case cost-effectiveness ratio of \$59,001 per Quality-Adjusted Life Year (QALY) (see Appendix for further details). The cost-effectiveness result is sensitive to the cost difference between analogs and traditional insulin, the cost of a hypoglycemic event, and the relative reduction in A1C that can be brought about by analogs. Despite this sensitivity, there are many reasons to believe that the technology may prove to be even more cost effective and valuable over time. For example, there are continual improvements in the clinical understanding and use of the drugs, as well as new findings regarding the additional benefits of blood glucose control in reducing macrovascular complications.<sup>6</sup>

#### *Convenience*

One of the major benefits of insulin analog use lies in patients' ability to maintain blood glucose control with fewer restrictions and limitations on their daily lives. There is a growing body of evidence that insulin analogs can significantly improve patients' treatment satisfaction and convenience by improving meal timing and reducing fear of hypoglycemia.<sup>7,8,9</sup> To date, these benefits have not been well quantified in terms of QALYs, and thus cannot be reflected in a cost-utility analysis of insulin analogs.

#### *From Convenience to Compliance*

Until a cure is developed, NEHI believes that some of the most significant advances in diabetes care will come in the form of improved management regimens that patients can easily adopt and maintain. Given the poor rate of adherence with management regimens in current diabetes care, innovations that allow a greater number of patients to enter into a treatment regimen may have significant societal value beyond what can be expressed in cost-effectiveness terms. Insulin analogs are extremely important in helping patients achieve higher levels of medication compliance.

#### *Evidence in Practice*

NEHI's modeling results suggest that the determination of value is dependent on relatively early assessments of the effectiveness of analog drugs. As such, more work needs to be done to confirm the benefits of combination use observed in initial trials. Despite this uncertainty, the wide adoption of this class of innovation in practice indicates that much of the health care community believes in the use of insulin analogs. Insurers pay for the analogs at the same level as regular insulins and there is evidence of broad adoption among clinicians.<sup>10,11</sup>



## SUMMARY

This report examines the value of biotechnology in the treatment of diabetes through a study of one of the most significant advancements in insulin therapy—insulin analogs. Applying cost-effectiveness analysis to the specific case of combination use of insulin analogs in type 1 patients, NEHI determined that insulin analog drugs used in combination therapy are indeed cost effective for type 1 diabetes patients. In addition to quantitative analysis, the qualitative evidence of improved patient convenience and quality of life indicate that insulin analogs offer significant value to patients.

Moving forward, health care decision makers need to find ways to quantitatively evaluate improvements in quality of life and patient convenience. These are critical measures that need to be incorporated in the larger analyses in order to provide a complete picture of the value of an innovation. In particular, health policy researchers need to create a mechanism to test the hypothesis that improved patient convenience leads to increased patient compliance and results in better clinical outcomes.