



## The Role of GLP-1 in the Treatment of Type 2 Diabetes

### Overview: Native GLP-1

Incretin hormones are those that cause an increase in the amount of insulin released from beta cells following ingestion of a meal.<sup>1</sup> In the pancreas, incretin hormones act to increase glucose-dependent insulin secretion from beta cells<sup>2</sup>; this action helps to ensure an appropriate insulin response after eating.<sup>1</sup> The most well-characterized incretin hormone is glucagon-like peptide-1 (GLP-1), which is considered to be the most important incretin released by the gut into the bloodstream in response to food.<sup>3</sup> In addition to its effects on insulin secretion after eating, GLP-1 also has additional effects that can help in the management of diabetes.<sup>3-5</sup>

The primary function of GLP-1 is to enhance insulin secretion only in the presence of elevated blood sugar (glucose) concentrations.<sup>3</sup> GLP-1 also suppresses the release of glucagon from the pancreas.<sup>4</sup> Glucagon stimulates glucose release from the liver<sup>6</sup>; so decreasing the amounts of glucagon helps to improve glucose control.<sup>3,4</sup> It is postulated that GLP-1 acts in the brain to reduce appetite<sup>4</sup> and in the stomach to slow the rate of gastric emptying so that nutrients are not absorbed too quickly into the bloodstream.<sup>5</sup> In addition, GLP-1 has been shown to improve acute beta-cell function in humans.<sup>3</sup>

In short, GLP-1 exerts multiple effects that contribute to the maintenance of glucose homeostasis:<sup>3-5</sup>

- Enhances glucose-dependent insulin secretion
- Suppresses inappropriate glucagon secretion
- Reduces appetite, leading to reduction of food intake
- Regulates the rate of gastric emptying, so that nutrients are not absorbed as quickly into the bloodstream

### GLP-1 and Type 2 Diabetes

People with type 2 diabetes may have reduced beta-cell function, which leads to relative insulin deficiency. They also often have inappropriately elevated levels of glucagon.<sup>7</sup> The elevated glucagon, which is produced in pancreatic alpha cells, causes the liver to release an excessive amount of glucose into the bloodstream, which then contributes to high blood glucose seen in type 2 diabetes.<sup>8</sup> Many people with diabetes may also have an accelerated rate of gastric emptying, which leads to increased nutrient delivery to the intestine resulting in an abnormally rapid rise in glucose following a meal.<sup>9</sup> The levels and actions of GLP-1 appear to be deficient in many people with type 2 diabetes, thus creating an opportunity for antidiabetes medications that act directly on the GLP-1 receptor or inhibit the breakdown of GLP-1 in the bloodstream.<sup>7</sup>

### GLP-1 Antidiabetes Treatments

Native human GLP-1 is rapidly inactivated by the dipeptidyl peptidase-4 (DPP-4) enzyme,<sup>10</sup> resulting in an extremely short half-life—approximately two minutes—in the blood.<sup>3</sup> The short half-life presents a challenge for its use as a therapeutic agent given the constraint around duration of action.<sup>11</sup> However, two treatment approaches have been developed to increase the amount of circulating GLP-1: GLP-1 receptor agonists and DPP-4 inhibitors.<sup>12</sup>

### ***GLP-1 Receptor Agonists***

Agonist versions of GLP-1 that have a longer half-life or are more potent can have therapeutic advantages.<sup>11</sup> An agonist is a molecule, such as a drug or a hormone, which binds to a receptor of a cell and triggers a response by that cell.<sup>13</sup> A GLP-1 receptor agonist binds to and activates the human GLP-1 receptor, the subsequent action of which leads to acutely enhanced beta-cell function and other effects, resulting in improved glucose control.<sup>3</sup> Also, GLP-1s have the potential to contribute to weight loss, unlike the weight gain that is commonly associated with insulin therapy and many oral diabetes medications.<sup>14</sup>

Recognizing the unique benefits of GLP-1 receptor agonists, the American Diabetes Association and the European Association for the Study of Diabetes (EASD) consensus panel updated the consensus treatment algorithm in late 2008 to include this class of antidiabetes medications for patients in whom either hypoglycemia is a concern or promotion of weight loss is a consideration.<sup>15</sup> In addition, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) consensus panel in October 2009 issued a new type 2 diabetes consensus treatment algorithm in which GLP-1 agonists are recommended for use earlier in the treatment continuum based on effectiveness and overall safety profile.<sup>16</sup>

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