

## Therapeutic Class Overview Incretin Mimetics

### Therapeutic Class

- Overview/Summary:** The glucagon-like peptide-1 (GLP-1) receptor agonists, or incretin mimetics, are one of two incretin-based therapies currently available for the management of type 2 diabetes. Specifically, albiglutide (Tanzeum<sup>®</sup>), dulaglutide (Trulicity<sup>®</sup>), exenatide (Bydureon<sup>®</sup>, Byetta<sup>®</sup>), and liraglutide (Victoza<sup>®</sup>) are Food and Drug Administration-approved as an adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes.<sup>1-5</sup> This medication class was developed to mimic the effects of endogenous GLP-1, a hormone that maintains glucose homeostasis through several different mechanisms. The incretin mimetics work by stimulating insulin secretion, inhibiting glucagon secretion, improving  $\beta$  cell responsiveness to glucose, delaying gastric emptying, and enhancing satiety. In addition, these agents increase insulin secretion from pancreatic  $\beta$  cells in the presence of elevated glucose concentrations. Therefore, due to the glucose-dependent manner in which the incretin mimetics work, the medication class is associated with a low risk of hypoglycemia compared to other antidiabetic agents.<sup>6</sup> The incretin mimetics are most commonly associated with gastrointestinal-related adverse events and all agents are associated with the risk of developing pancreatitis. Only albiglutide, dulaglutide, exenatide extended-release, and liraglutide have boxed warnings regarding the risk of thyroid C-cell tumors. The incretin mimetics are available as subcutaneous injections. Albiglutide, dulaglutide and exenatide ER is administered once-weekly (independent of meals), exenatide IR is administered twice-daily (60 minutes before meals) and liraglutide is administered once-daily (independent of meals).<sup>1-5</sup> There are currently no generic incretin mimetics available.

**Table 1. Current Medications Available in Therapeutic Class<sup>1-5</sup>**

| Generic (Trade Name)                                     | Food and Drug Administration Approved Indications*   | Dosage Form/Strength   | Generic Availability |
|--|--|--|----------------------|
| Albiglutide (Tanzeum <sup>®</sup> )                      | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus | Pre-filled pen powder (solution) for Injection:<br>30 mg<br>50 mg  | -                    |
| Dulaglutide (Trulicity <sup>®</sup> )                    | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus | Solution for injection (pen or syringe):<br>0.75 mg/0.5 mL<br>1.5 mg/0.5 mL  | -                    |
| Exenatide (Bydureon <sup>®</sup> , Byetta <sup>®</sup> ) | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus | Extended-release powder (suspension) for injection (Bydureon <sup>®</sup> ; pen or dual chamber pen):<br>2 mg<br><br>Solution for injection (Byetta <sup>®</sup> ; pen):<br>250 $\mu$ g/mL | -                    |
| Liraglutide (Victoza <sup>®</sup> )                      | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus | Solution for Injection (pen):<br>6 mg/mL   | -                    |

\* Consider reducing the dosage of concomitantly administered insulin secretagogues (e.g., sulfonylureas) and/or insulin to reduce the risk of hypoglycemia.

### Evidence-based Medicine

- In general, the incretin mimetics have been evaluated in clinical trials as add-on therapy to treatment regimens of established antidiabetic agents. Data consistently demonstrate that incretin mimetics are

associated with positive effects on glycosylated hemoglobin (HbA<sub>1c</sub>), fasting plasma glucose (FPG), post-prandial glucose (PPG), and body weight. In addition, glycemic goals were consistently achieved when an incretin mimetic was added to existing treatment regimens.<sup>7-59</sup>

- When compared to other antidiabetic agents (metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, insulin therapy), efficacy data are not consistent, with the incretin mimetics achieving superiority or comparable benefits in glycemic outcomes. However, in general, all incretin-based therapies, including the incretin mimetics, consistently demonstrate a beneficial effect on body weight compared to other antidiabetic agents.<sup>7-59</sup>
- Safety and efficacy of dulaglutide has been evaluated in an extensive clinical trials program including monotherapy trials, add-on therapy to metformin, metformin and sulfonylurea, pioglitazone and insulin (with or without metformin).<sup>7-12</sup>
  - The 52-week double-blind AWARD-3 study of patients inadequately treated with diet and exercise, or with diet and exercise and one anti-diabetic agent used at submaximal dose (N=807). At week 26, noninferiority in reduction of hemoglobin A1c (HbA<sub>1c</sub>) was demonstrated between dulaglutide and metformin for both the 0.75 mg weekly and 1.5 mg weekly doses (-0.7% and -0.8% vs. -0.6%, respectively).<sup>7</sup>
  - AWARD-1 was a 52-week placebo-controlled study that evaluated dulaglutide safety and efficacy as an add-on to maximally tolerated doses of metformin (≥1500 mg per day) and pioglitazone (up to 45 mg per day) (N=976). At 26 weeks, treatment with dulaglutide 0.75 mg and 1.5 mg once weekly resulted in a statistically significant reduction in HbA<sub>1c</sub> compared to placebo (-0.8% and -1.1 placebo corrected difference, respectively; P<0.001 for both comparisons) and compared to exenatide (-0.3% and -0.5 exenatide-corrected difference, respectively; P<0.001 for both comparisons).<sup>12</sup>
- Albiglutide was compared in a non-inferiority trial with liraglutide. Albiglutide effectively reduced HbA<sub>1c</sub>; however, based upon the prespecified non-inferiority parameters, the criteria for non-inferiority of albiglutide were not met. The HbA<sub>1c</sub> treatment goal of <7.0% was achieved by 42% of albiglutide-treated patients and 52% of liraglutide-treated patients (P=0.0023), while the goal of HbA<sub>1c</sub> lower than 6.5% was achieved by 20% of albiglutide-treated patients and 28% of liraglutide-treated patients (P=0.0009).<sup>14</sup>
- Few head-to-head clinical trials within the class have been conducted. Compared to exenatide, exenatide extended-release significantly decreased HbA<sub>1c</sub>, and achieved similar decreases in body weight.<sup>30,37</sup> In a single trial, liraglutide significantly decreased HbA<sub>1c</sub> compared to exenatide. Furthermore, liraglutide significantly decreased FPG while exenatide significantly decreased PPG.<sup>45</sup>
- In a 26-week open-label trial, there was a significantly greater reduction from baseline in HbA<sub>1c</sub> at 26 weeks for patients treated with liraglutide compared to exenatide extended-release (-0.21%; 95% confidence interval [CI], -0.08 to -0.33). In addition, significantly more patients receiving liraglutide achieved an HbA<sub>1c</sub> <7.0% compared to patients treated with exenatide extended-release (60 vs 53%; P=0.0011). Reductions in bodyweight also favored treatment with liraglutide (-0.90 kg; 95% CI, -0.39 to -1.40).<sup>38</sup>

### **Key Points within the Medication Class**

- According to Current Clinical Guidelines:
  - Type 2 diabetes: <sup>60-66</sup>
    - Metformin remains the cornerstone to most antidiabetic treatment regimens.
    - Patients with high glycosylated hemoglobin will most likely require combination or triple therapy in order to achieve glycemic goals.
    - The incretin mimetics are recommended as a potential second-line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals.
      - A lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing post-prandial glucose, and the potential for weight loss are noted as advantages associated with the incretin mimetics compared to other classes of antidiabetic agents.<sup>60-66</sup>

- No one incretin mimetic is recommended or preferred over another. <sup>52-57</sup>
- Other Key Facts:
  - Albiglutide, dulaglutide and exenatide ER is administered once-weekly (independent of meals). <sup>1-3</sup>
  - Exenatide IR is administered twice-daily (60 minutes before meals). <sup>4</sup>
  - Liraglutide is administered once-daily (independent of meals). <sup>5</sup>
  - No generic incretin mimetics are available.

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