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®), dulaglutide (Trulicity®), exenatide (Bydureon®, Byetta®), and liraglutide (Victoza®) are Food and Drug Administration-approved as an adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes.¹⁻⁵ 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 β cell responsiveness to glucose, delaying gastric emptying, and enhancing satiety. In addition, these agents increase insulin secretion from pancreatic β 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.⁶ 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).¹⁻⁵ There are currently no generic incretin mimetics available.

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

* 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 (HbA1c), 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.7-59

- 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.7-59

- 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).7-12
  - 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 (HbA1c) 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).7
  - 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 HbA1c 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).12

- Albiglutide was compared in a non-inferiority trial with liraglutide. Albiglutide effectively reduced HbA1c, however, based upon the prespecified non-inferiority parameters, the criteria for non-inferiority of albiglutide were not met. The HbA1c 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 HbA1c lower than 6.5% was achieved by 20% of albiglutide-treated patients and 28% of liraglutide-treated patients (P=0.0009).14

- Few head-to-head clinical trials within the class have been conducted. Compared to exenatide, exenatide extended-release significantly decreased HbA1c, and achieved similar decreases in body weight.30,37 In a single trial, liraglutide significantly decreased HbA1c compared to exenatide. Furthermore, liraglutide significantly decreased FPG while exenatide significantly decreased PPG.45

- In a 26-week open-label trial, there was a significantly greater reduction from baseline in HbA1c 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 HbA1c <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).38

**Key Points within the Medication Class**

- According to Current Clinical Guidelines:
  - Type 2 diabetes: 60-66
    - 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. 60-66
Therapeutic Class Overview: incretin mimetics

- No one incretin mimic is recommended or preferred over another. 52-57

Other Key Facts:
  - Abbiglutide, dulaglutide and exenatide ER is administered once-weekly (independent of meals). 1-3
  - Exenatide IR is administered twice-daily (60 minutes before meals). 4
  - Liraglutide is administered once-daily (independent of meals). 5
  - No generic incretin mimetics are available.

References
40. Marre M, Shaw J, Brandle M, Bebaker MMK, Kamarudin NA, Strand J, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycemic control and weight compared to adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabet Med. 2009;26:268-78.