<table>
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<th>Program Name</th>
<th>GLP-1 Receptor Agonists: Once Weekly Options for the Management of Type 2 Diabetes</th>
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<tr>
<td>Planning Committee</td>
<td>Dr. Harpreet Bajaj MD, MPH, ECNU, FACE</td>
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<tr>
<td></td>
<td>Andrea Main B.Sc Phm, CDE</td>
</tr>
<tr>
<td></td>
<td>Lyne Gauthier B.Pharm, M.Sc</td>
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<td>Accreditation Information</td>
<td>This version of the program is unaccredited and intended for informational purposes only. An accredited version is available online at <a href="http://www.rxBriefCase.com">www.rxBriefCase.com</a> until January 12, 2017</td>
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<tr>
<td>Sponsor</td>
<td>This case study is supported by an educational grant from Eli Lilly Canada</td>
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Learning Objectives
Upon completion of the lessons, participants will be able to

- Describe the glucagon-like peptide 1 receptor (GLP-1R) agonists available in Canada for the treatment of type 2 diabetes.
- Compare the daily and weekly GLP-1R agonists
- Recognize clinical situations where a GLP-1R agonists could be used for patients with type 2 diabetes
- Consider patient and agent characteristics when individualizing the choice of GLP-1R agonists for patients with type 2 diabetes
- Identify and address potential barriers when advancing to injectable therapy in patients with type 2 diabetes

Pre/Post-Course Survey
a) Please rate your level of knowledge of the daily administered GLP-1 receptor agonists currently available in Canada (1 = limited, 5= excellent).

b) Please rate your level of knowledge of the weekly administered GLP-1 receptor agonists that are newly available in Canada (1 = limited, 5= excellent).

c) How often do you recommend GLP-1 receptor agonists as add on therapy to metformin when patients remain above blood glucose targets (1=never, 5 = always)?

d) How comfortable are you with training patients on how to use the self-injection devices used to administer GLP-1 receptor agonists (1=completely uncomfortable, 5 = completely comfortable)?

e) Please rate your level of knowledge of the evidence of clinical efficacy of the GLP-1 receptor agonists (1 = limited, 5= excellent).

f) Please rate your knowledge of the evidence of safety of the GLP-1 receptor agonists (1 = limited, 5= excellent).

Meet Tom
Tom is 55 years old and has an eight year history of type 2 diabetes. Tom is a heavy duty mechanic and works long hours, often overtime. He is married, does not smoke and drinks socially. Tom is obese and finds it difficult to engage in physical activity and adhere to dietary recommendations due to his current work schedule. Tom consistently remains above his glycemic targets with his A1c ranging from 7.5% to 8.0% over the past year and complains of craving sugar and carbohydrate rich foods. Tom has taken sulfonylureas and other oral
agents in the past, but had issues with tolerability due to hypoglycemia and other adverse effects. Currently, Tom is taking metformin (850 mg twice daily) and sitagliptin (100mg daily). His clinical assessment includes the following:

**BMI**: 31.4 kg/m²  
**Waist circumference**: 110 cm  
**Blood pressure**: 135/85 mm Hg  
**LDL-C**: 2.0 mmol/L  
**A1C**: 7.9%  
**eGFR**: 75 mL/min

Tom tells you that he has heard about some new medications for diabetes from his doctor that can help you lose weight by controlling your appetite, but is skeptical about them as he does not like the idea of having to inject medication. As well, Tom wonders how effective these medications are and if his diabetes is severe enough that he would need an injectable medication.

**Case Question**  
Does Tom require a change to his pharmacotherapy for type 2 diabetes?  
- a) Yes  
- b) No

**Treatment Intensification in Type 2 Diabetes**  
The importance of achieving glycemic targets in type 2 diabetes is essential to reducing the risk of complications. While lifestyle management is the cornerstone of management of type 2 diabetes, the most recent guidelines from the Canadian Diabetes Association recommend initiating pharmacotherapy should glycemic targets not be reached within two to three months in patients with A1c of less than 8.5%, and initiating pharmacotherapy immediately in those individuals with higher A1c (Figure 1). Metformin is recommended as the drug of first choice for the management of type 2 diabetes, regardless of whether an individual is overweight. If glycemic targets are not achieved within three to six months of treatment, the addition of another class of antihyperglycemic is recommended. The selection of pharmacotherapy for treatment intensification is individualized based upon:

- **Patient characteristics:**  
  - Degree of hyperglycemia  
  - Presence of comorbidities  
  - Patient preference and ability to access treatments

- **Properties of the treatment:**  
  - Effectiveness and durability of lowering blood glucose  
  - Risk of hypoglycemia  
  - Effectiveness in reducing diabetes complications  
  - Effect on body weight  
  - Side effects  
  - Contraindications  
  - Cost and coverage
**Figure 1** outlines the recommended approach to the management of type 2 diabetes in the most recent guidelines from the Canadian Diabetes Association.

![Diagram](image)

**Pharmacologic Management of Type 2 Diabetes - 2015 Interim Update**

Source: Canadian Diabetes Association. Pharmacologic Management of Type 2 Diabetes - 2015 Interim Update.

The Canadian Diabetes Association guidelines recommend incretin agents as one option for add-on therapy to metformin. Two categories of incretin agents are available in Canada: the GLP-1R agonists and the dipeptidyl peptidase 4 (DPP4) inhibitors. Two short acting GLP-1R agonists, liraglutide and exenatide, have been available in Canada since 2010 and 2011 respectively, for the treatment of type 2 diabetes. More recently, three long acting GLP-1R agonists that are dosed on a once weekly basis have become available in Canada, providing a unique pharmacological alternative for the management of type 2 diabetes.

The Canadian Diabetes Association guidelines recommend timely adjustments to medication regimens, with a goal of achieving target A1c within 3 to 6 months.

**Mechanism of Action – GLP-1R Agonists**

**Test Yourself**
Which of the following hormones mediate the “incretin effect”?

- a) Glucose dependent insulinotropic polypeptide (GIP)
- b) Glucagon like peptide 1 (GLP-1)
- c) Sodium-glucose cotransporter-2 (SGLT2)
- d) A and B
- e) All of the above

GLP-1R agonists are subcutaneously administered exogenous peptides that exert their therapeutic effects by mimicking the actions of GLP-1 in the body. When glucose is taken orally, the amount of insulin secreted in response is greater than if the same glucose load was taken intravenously. Two hormones, glucose dependent insulinotropic polypeptide (GIP) and glucagon like peptide 1 (GLP-1), mediate this phenomenon, which is referred to as the “incretin effect.” GLP-1 levels are very low in the fasting state and rise within minutes of ingesting food, thereby stimulating the secretion of insulin and inhibiting the secretion of glucagon. Typically, up to 70% of the insulin response to a meal is attributed to GIP and GLP-1. GLP-1 receptors are found in the pancreas, lung, heart, blood vessels, gastrointestinal tract, kidney, breast and central nervous system. In the pancreas, binding of GLP-1 to GLP-1 receptors stimulates the secretion of insulin and inhibits the secretion of glucagon. In the gastrointestinal tract, GLP-1 decreases motility, which delays gastric emptying, which helps to normalize post-prandial glucose levels. As well, GLP-1 promotes satiety. Individuals with type 2 diabetes tend to have a poor incretin effect.

The body’s naturally occurring GLP-1 has a half-life of only about two minutes as it is rapidly broken down by dipeptidyl peptidase 4 (DPP-4). As such, the therapeutic value of administering exogenous GLP-1 in its naturally occurring form is limited. However, longer acting GLP-1 receptor agonists (GLP-1R agonists) that have been formulated to be resistant to breakdown by DDP-4 are of therapeutic benefit for the management of type 2 diabetes, by activating the GLP-1 receptor.
**Formulation of GLP-1R Agonists**

**Test Yourself**

Which of the following GLP-1R agonists are based on human GLP-1 with some modifications such as altering the peptide’s amino acid sequence or adding side chains.

a) Albiglutide  
b) Dulaglutide  
c) Exenatide  
d) A and B  
e) All of the above

There are five GLP-1R agonists currently available in Canada approved for the treatment of type 2 diabetes, two daily administered (exenatide BID and liraglutide once daily) and three once weekly administered options (albiglutide, dulaglutide, and exenatide once weekly). GLP-1R agonists can be categorized as being either human GLP-1 based or exendin-4 based (Exendin-4 is a molecule that was isolated from the saliva of the Gila monster). GLP-1R agonists used in the management of type 2 diabetes are designed to be more resistant to degradation by DPP-4, with this being accomplished using different strategies depending on the product. Altering the amino acid sequence of the peptide to make it more resistant to degradation by DPP-4 is one such approach. Other approaches include adding side chains or fusing the GLP-1R agonist to a carrier molecule that alters the drug’s pharmacokinetics without changing its ability to interact with its receptor.
Liraglutide, dulaglutide and albiglutide are all human-based GLP-1R agonists. Liraglutide has a once daily dosing. Dulaglutide and albiglutide are once weekly administered GLP-1R agonists that became available in Canada in 2015. For both drugs, the extended duration is achieved through alterations in the amino acid sequence of the peptide and the addition of carrier molecules (Table 1).

Exenatide is an exendin-4 based GLP-1 receptor agonist that is considered a shorter acting agent. Its sequence shares a 53% identity with human GLP-1 and it has a relatively short-half life (approximately 2.4 hours), which results in large fluctuations in GLP-1 levels as it is administered on a twice daily basis and subject to rapid elimination. Exendin-4 activates the GLP-1 receptor with a potency similar to that of native GLP-1. Exenatide is also now available in a once weekly, extended release formulation in which exenatide is encapsulated in 0.06mm microspheres. After suspension and injection subcutaneously, the microspheres hydrate at the injection site and form an amalgam by adhering to one another. Approximately 1% of the exenatide at the surface is released in the first few hours following injection. The deeper exenatide continues to diffuse over the next two weeks, reaching a peak concentration during this time.

Recently developed GLP-1R agonists have alterations in their structures that prolong the half-life to 5 to 14 days, which permits once weekly, subcutaneous administration.

**Table 1:** Summary of GLP-1R Agonists Available in Canada Approved for Use in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Agent</th>
<th>Human or Exendin Based</th>
<th>Modification to Extend Duration of Action</th>
<th>Dosing*</th>
<th>(T_{1/2}) and (T_{max})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albiglutide</td>
<td>Human</td>
<td>Alteration in amino acid sequence and fusion to carrier molecule (albumin)</td>
<td>30 mg subcutaneously once weekly. The dose may be increased to 50 mg once-weekly based on individual glycemic response. Can be used any time of day, with or without meals</td>
<td>(T_{1/2}: \sim 5) days (T_{max}: 3–5) days</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Human</td>
<td>Alteration in amino acid sequence and fusion to carrier molecule (Fc fragments of immunoglobulin G)</td>
<td>Initiated with a dose of 0.75 mg subcutaneously once weekly at any time of day. Dose can be increased to 1.5 mg subcutaneously once weekly for additional glycemic control if needed. Can be used any time of day, with or without meals</td>
<td>(T_{1/2}: \sim 5) days (T_{max}: 24–72) hours</td>
</tr>
<tr>
<td>Exenatide BID</td>
<td>Exendin Based</td>
<td>Alteration in amino acid sequence</td>
<td>Administered at any time within the 60-minute period before the morning and</td>
<td>(T_{1/2}: 2.4) hours</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Species</td>
<td>Alteration in Amino Acid Sequence</td>
<td>Dosing Method</td>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------</td>
<td>-----------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>------------------</td>
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<tr>
<td>Exenatide once weekly&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Exendin Based</td>
<td>Alteration in amino acid sequence and encapsulation in microspheres</td>
<td>2mg subcutaneously once weekly. Can be used any time of day, with or without meals</td>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;: 7–14 days</td>
</tr>
<tr>
<td>Liraglutide&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Human</td>
<td>Alteration in amino acid sequence and addition of 16 carbon fatty acid chain</td>
<td>Initiated with a dose of 0.6 mg subcutaneously once daily for at least one week. After one week at 0.6 mg per day, the dose should be increased to 1.2 mg once daily. Based on clinical response and after at least one week the dose can be increased to 1.8 mg once daily to achieve maximum efficacy for glycemic control. Dosed without regards to food or meals.</td>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;: ~13 hours</td>
</tr>
</tbody>
</table>
Clinical Efficacy of Once Weekly GLP-1R Agonists

Test Yourself

Based on randomized clinical trials comparing once-weekly GLP-1R agonists to Liraglutide, which of the following is non-inferior for A1c reduction?

a. Albiglutide
b. Dulaglutide
c. Exenatide once weekly
d. All of the above

The clinical trial programs of albiglutide, dulaglutide and exenatide once weekly were all extensive, involving numerous randomized controlled trials (RCTs) in which once weekly GLP-1R agonists were evaluated as monotherapies and combination therapies, with comparison to placebo, DPP-4 inhibitors, glitazones, sulfonylureas, long-acting insulins and GLP-1R agonists. A brief overview of the results of these clinical trial programs is summarized in Table 2, as well a more detailed reporting of head-to-head comparative studies between GLP-1R agonists (Table 3). Further details of the trials can be found in the linked documents of the Resources section of this lesson.

Table 2: Summary of Clinical Trial Programs of Once Weekly Administered GLP-1R Agonists Available in Canada

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trials</th>
<th>Summary of Efficacy Results</th>
<th>Summary of Adverse Effects</th>
</tr>
</thead>
</table>
| Albiglutide | HARMONY 1 to 8 | Reductions in A1c of 0.55% to 0.90%  
- Superior to placebo, sitagliptin, and glimepiride  
- Noninferior to insulin lispro and insulin glargine  
- Failed to meet noninferiority to liraglutide and pioglitazone.  
Changes in weight ranged from +0.28 to -1.21 kg.  
Generally favorable effect on weight, but possibly less pronounced than with other GLP-1R agonists. | Nausea (4.8–13%)  
Vomiting (1.6–7%)  
Symptomatic hypoglycemia  
- 1–3% with albiglutide alone or added to metformin  
- 10.4–32.6% when added to sulfonylurea or basal insulin therapy |
| Dulaglutide | AWARD 1 to 6 | Reductions in A1c of 0.76–1.64%  
- Superior to placebo, metformin, sitagliptin, exenatide BID, and insulin glargine.  
- Non-inferior to liraglutide | Nausea (8% to 28%)  
Vomiting (4% to 17%)  
Symptomatic hypoglycemia  
- 5% to 11%  
|
Changes in weight ranged from -0.86 to -3.03 kg.

Reducions in A1c of -1.3 –2.0%.
- Superior to exenatide BID, pioglitazone, sitagliptin, insulin glargine
- Failed to achieve non-inferiority to liraglutide

Nausea (9% to 26%)
Vomiting (4% to 11%)
Symptomatic hypoglycemia
- 2% without sulfonylurea
- 16% with sulfonylurea

Table 3 summarizes the A1c lowering effects of GLP-1R agonists from head-to-head comparative trials between agents. In all studies, GLP-1R agonists were given as add-on therapy to oral medications. The average baseline A1c ranged from approximately 8.0 to 8.5%, depending on the study. In a head-to-head comparison of albiglutide and liraglutide, A1c lowering was statistically significantly greater with liraglutide. In the DURATION -6 study, exenatide once weekly failed to demonstrate non-inferiority to liraglutide, despite it being superior to exenatide twice daily in other trials. Dulaglutide, however, was found to be non-inferior to liraglutide and superior to exenatide twice daily.

Table 3: Summary of head-to-head comparisons of GLP-1R agonists

<table>
<thead>
<tr>
<th>GLP-1R Agonist</th>
<th>Study</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albiglutide</td>
<td>HARMONY-7 study</td>
<td>Patients were randomized to either albiglutide 50 mg once weekly or liraglutide 1.8 mg once daily as add on therapy to other oral agents. A1c lowering was greater with liraglutide (1.0%) than with albiglutide (0.8%)</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>AWARD-1 Study</td>
<td>Patients were randomized to dulaglutide 0.75mg once weekly, dulaglutide 1.5mg once weekly or exenatide 10 mcg BID as add on therapy to metformin and pioglitazone. Both dosages of dulaglutide were statistically superior to exenatide BID in terms of A1c lowering: o Dulaglutide 0.75mg: -1.3% o Dulaglutide 1.5mg: -1.5% o Exenatide 10 mcg BID: -1.0%</td>
</tr>
<tr>
<td></td>
<td>AWARD-6 Study</td>
<td>Patients were randomized to either dulaglutide 1.5mg once weekly or liraglutide 1.8mg once daily as add on therapy to metformin. A1c lowering was 1.4% in both groups, demonstrating noninferiority of dulaglutide to liraglutide.</td>
</tr>
</tbody>
</table>
Exenatide Once Weekly

Duration-1 Study\textsuperscript{17} • Patients were randomized to exenatide 2mg once weekly or 10 mcg twice daily as add on therapy to diet or oral medications.
• Exenatide once weekly was found to be superior to twice daily exenatide for A1c lowering (1.9% versus 1.5%)

Duration-5 Study\textsuperscript{21} • Patients were randomized to exenatide 2mg once weekly or 10 mcg twice daily as add on therapy to diet or oral medications.
• Exenatide once weekly was found to be superior to twice daily exenatide for A1c lowering (1.6% versus 0.9%)

Duration-6 Study\textsuperscript{22} • Patients were randomized to either exenatide 2mg once weekly or liraglutide 1.8mg once daily as add on therapy to metformin with sulfonylurea or pioglitazone.
• A1c lowering with exenatide once weekly was 1.3% compared with 1.5% for liraglutide, failing to demonstrate noninferiority of exenatide QW.

The daily and weekly administered GLP-1R agonists are approved by Health Canada for combination therapy with metformin, sulfonylurea and different insulins for the treatment of type 2 diabetes (Table 4). They are not approved for use in type 1 diabetes.

Table 4: Approved Indications for GLP-1R Agonists Available in Canada Approved for Use in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Agent</th>
<th>Health Canada Approved Indications for Type 2 Diabetes</th>
</tr>
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<tbody>
<tr>
<td>Daily Administered Agents</td>
<td></td>
</tr>
<tr>
<td>Exenatide BID\textsuperscript{8}</td>
<td>Indicated in combination with</td>
</tr>
<tr>
<td></td>
<td>• Metformin, and/or a sulfonylurea to improve glycemic control in patients with type 2 diabetes mellitus, when maximally tolerated doses of these oral therapies in addition to diet and exercise do not provide adequate glycemic control.</td>
</tr>
<tr>
<td></td>
<td>• In combination with insulin glargine (with or without metformin) to improve glycemic control in patients with type 2 diabetes mellitus when insulin glargine (with or without metformin) in addition to diet and exercise, does not provide adequate glycemic control.</td>
</tr>
<tr>
<td>Liraglutide\textsuperscript{9}</td>
<td>Indicated for once-daily administration for the treatment of adults with type 2 diabetes to improve glycemic control in combination with:</td>
</tr>
<tr>
<td></td>
<td>• Metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control.</td>
</tr>
<tr>
<td></td>
<td>• Metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control.</td>
</tr>
<tr>
<td></td>
<td>• Metformin and a basal insulin, when diet and exercise plus dual therapy with liraglutide and metformin do not achieve adequate glycemic control.</td>
</tr>
<tr>
<td>Once Weekly Administered Agents</td>
<td></td>
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</table>
| **Albiglutide**<sup>11</sup> | Once-weekly administration for the treatment of adults with type 2 diabetes mellitus, as an adjunct to diet and exercise to improve glycemic control  
  - As monotherapy in patients inadequately controlled by diet, exercise and when metformin is inappropriate due to contraindication or intolerance.  
  - In combination with one of the following therapeutic options in patients who have not achieved adequate glycemic control:  
    - Metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control.  
    - Metformin and sulfonylurea, when diet and exercise plus dual therapy with metformin and sulfonylurea do not achieve adequate glycemic control.  
    - Basal insulin with oral antidiabetic therapies, when diet and exercise plus basal insulin with oral antidiabetic therapies do not achieve adequate glycemic control. |
| **Dulaglutide**<sup>10</sup> | Treatment of adult patients with type 2 diabetes mellitus to improve glycemic control, in combination with:  
  - Diet and exercise in patients for whom metformin is inappropriate due to contraindication or intolerance.  
  - Metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control.  
  - Metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control.  
  - Prandial insulin with metformin, when diet and exercise plus basal or basal-bolus insulin therapy (up to two injections of basal or basal plus prandial insulin per day) with or without oral antihyperglycemic medications, do not achieve adequate glycemic control. |
| **Exenatide Once Weekly**<sup>12</sup> | Monotherapy:  
  - As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance.  
  Combination with metformin:  
  - Indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin when metformin used alone, with diet and exercise, does not provide adequate glycemic control.  
  Combination with a sulfonylurea:  
  - Indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with a sulfonylurea when the sulfonylurea used alone, with diet and exercise, does not provide adequate glycemic control.  
  Combination with metformin and a sulfonylurea:  
  - Indicated in patients with type 2 diabetes mellitus to improve glycemic control. |
control in combination with metformin and a sulfonylurea when dual therapy with these two agents, with diet and exercise, does not provide adequate glycemic control.

Additional Benefits of GLP-1R Agonists

Test Yourself
The use of GLP-1R agonists is associated with weight gain.

a) True
b) False

Weight Loss
GLP-1R agonists delay gastric emptying and promote the feeling of satiety. In addition to their glucose lowering effects, the GLP-1R agonist use is also associated with weight loss. In clinical trials of the once weekly GLP1-R agonists patients experienced varying degrees of weight loss (assessed after 24 to 32 weeks of follow-up): 2

- Albiglutide: +0.3 to -1.2 kg
- Dulaglutide: -0.9 to -3.0 kg
- Exenatide once weekly: -2.0 to -3.7 kg

Similar weight loss was reported in a head-to-head comparison of liraglutide (–3.24 kg) versus exenatide twice daily (–2.87 kg). 2

While nausea is a common adverse effect of the GLP-1R agonists, weight loss associated with GLP-1R agonist use appears to be independent of this effect. Nausea tends to resolve within about six to eight weeks of treatment, but the effect of GLP-1R agonists in promoting weight loss is more prolonged, suggesting the reduced food intake with GLP-1Rs is not directly attributable to nausea. 2 Albiglutide appears to be less efficacious in promoting weight loss than some other agents. It has been suggested that this is due to a reduced ability to promote satiety, potentially because of its large molecular size which prevents it from entering the blood brain barrier. As well, albiglutide has a reduced effect on gastric motility, which may also contribute to its variable efficacy in promoting weight loss. 2

Hypoglycemia

Test Yourself
The risk of hypoglycemia with the GLP-1R agonists is higher when they are used in combination with sulfonylureas or basal insulin.

a) Sulfonylureas
b) Basal insulin
c) Both sulfonylureas and basal insulin
d) None of the above

The risk of hypoglycemia is relatively low with the GLP-1R agonists, with rates of minor hypoglycemia ranging from
- Abiglutide: 1% to 17%<sup>11,37</sup>
- Dulaglutide: 5 to 11%<sup>15</sup>
- Exenatide once weekly: 2.8% to 12%<sup>38</sup>

The ranges above may include monotherapy, combination therapy with metformin, or combination with sulfonylurea or insulin. Importantly, the high end of the ranges reflect the risk of hypoglycemia when GLP-1R agonists are used in combination with a sulfonylurea or basal insulin, not the risk with monotherapy or combination therapy with metformin.<sup>2</sup> For example, approximately 2% to 3% of patients experience hypoglycemia while on albiglutide alone or in combination with metformin, but this increases to 16% to 17% when albiglutide is added to a sulfonylurea or basal insulin therapy.<sup>11</sup> Of note, cases of severe or major hypoglycemia are rare with the GLP-1R agonists.

Rates of hypoglycemia with exenatide twice daily in clinical trials ranged from 4.5% to 35.7%, again with the higher rates being observed in combination with a sulfonylurea.<sup>8</sup> For liraglutide, rates of hypoglycemia in clinical trials ranged from 0.8% to 27.4%, with the addition of liraglutide to a sulfonylurea increasing the risk.<sup>9</sup>

Revisit Tom
You explain to Tom that his most recent A1c value of 7.9% is above target and places him at risk for long-term complications of diabetes. You discuss with Tom the benefits of GLP-1R agonists, in particular their potential for A1c lowering and for weight loss. As well, you let Tom know that a GLP-1R agonist would replace his sitagliptin (it would not be used in combination) so this could potentially simplify his medication regimen if a once weekly administered option was used, in addition to his metformin. Tom remains hesitant about the medication class. He has also heard from a friend that this medication class will make him nauseated and that the administration is too complicated.

Test Yourself
Nausea with the once weekly administered GLP-1R agonists

a) Tends to resolve with continued treatment for six to eight weeks.
b) Tends to resolve with continued treatment after one week.
c) Is thought to be associated with reduced gastric emptying
d) A and C
e) B and C

Other Adverse Effects of Once Weekly GLP-1R Agonists
Gastrointestinal Effects
The most common adverse effects of the GLP-1 inhibitors affect the gastrointestinal (GI) tract and include dose-dependent nausea (mild to moderate), vomiting and diarrhea.<sup>4,39</sup> Nausea is a common adverse effect of both the daily and weekly administered GLP-1R agonists (Table 5), but tends to be higher with exenatide BID due to its relatively short duration of action and resulting fluctuations in concentration.<sup>4</sup> Nausea is thought to relate to the reduced gastric emptying that occurs with GLP-1R agonists.<sup>6</sup> Adverse GI effects do tend to decline over time, typically resolving within the first six to eight weeks of treatment.<sup>6</sup> Nausea with exenatide BID may resolve more slowly than with the longer acting, once daily and once weekly administered products.<sup>45</sup> Starting at a lower dose and titrating upward can also reduce the incidence of nausea, although the ability to do so depends on the individual agent.<sup>6</sup>
Exenatide once weekly, for example, has a fixed dosage that does not allow for titration to improve its GI tolerability.

**Table 5:** Frequency of nausea and vomiting with GLP-1R agonists\(^6,9,13,14,15,16\)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Nausea</th>
<th>Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily Administered Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide BID</td>
<td>33% to 57%</td>
<td>12% to 17%</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>10% to 47%</td>
<td>4% to 17%</td>
</tr>
<tr>
<td><strong>Once Weekly Administered Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albiglutide</td>
<td>4.8% to 13%</td>
<td>3% to 6%</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>8% to 28%</td>
<td>4% to 17%</td>
</tr>
<tr>
<td>Exenatide once weekly</td>
<td>5% to 27%</td>
<td>4% to 11%</td>
</tr>
</tbody>
</table>

**Pancreatitis and Pancreatic Cancer**

GLP-1R agonists have warnings and precautions regarding a possible link to pancreatitis, although there is conflicting evidence about this link as diabetes itself may be a risk factor for pancreatitis.\(^39\) In addition, there is an ongoing debate about the association between GLP-1R agonists with pancreatic cancer.\(^4\) Statements about this issue from some of the major drug regulatory bodies can be found at the links below:

- **European Medicines Agency**
- **Health Canada**
- **United States Food and Drug Administration**

Since issuing these statements, the Food and Drug Administration and the European Medicines Agency have both evaluated multiple data sources and agree that the data is inconsistent with respect to a causal association between the GLP1-R agonists and pancreatitis or pancreatic cancer.\(^46\) They have not reached a final conclusion; however, the evidence to date has been reassuring.\(^46\)

**MTC and MEN2**

GLP-1R agonists are contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2).\(^39\) These contraindications are due to an increased incidence of C-cell hyperplasia and tumors in rodents in preclinical trials. However, these findings have not been replicated in humans or primates and may relate to higher concentrations in GLP-1 receptors on rodent C-cells.\(^39\)

**Injection Site Reactions**

Injection site reactions are another adverse effect of the GLP-1R agonists. While no head-to-head comparisons exist between the three once weekly GLP-1R agonists, injection site reactions were reported more frequently with exenatide once weekly, an exendin-based product that has 53% homology with human GLP-1, than with the human-based GLP-1R agonists, dulaglutide and liraglutide.\(^39\) Further, while exenatide once weekly appears to be more effective in A1c lowering than the twice daily
administered product, it may be more immunogenic, with a greater proportion of patients in head-to-head clinical trials reporting rash and pruritus at the injection site with exenatide once weekly (4.7% to 20.9%) than exenatide twice daily (0.8% to 2.1%). Based upon pooled data from clinical trials, injection site reaction for the other GLP-1R agonists were as follows:

- Albiglutide – 13.1%
- Dulaglutide – 1.7% to 1.9%
- Liraglutide – 2%

Educate patients regarding the possibility of localized irritation or nodule formation at injection site. Rotating of the injection site between the abdomen, thighs, and upper arms may reduce the risk of injection site reactions with the GLP-1R agonists.

**Gastroparesis**

The GLP-1R agonists have not been studied in patients with gastroparesis, but due to their effects on gastric emptying, they are not recommended in patients with gastroparesis according to their approved labelling.

**Renal Impairment**

Dosage adjustments for the GLP-1R agonists may be required in patients in renal dysfunction (Table 6).

**Table 6**: Dosing of GLP-1R Agonists in Renal Dysfunction

<table>
<thead>
<tr>
<th>Agent</th>
<th>eGFR ≥ 30 mL/min</th>
<th>eGFR &lt; 30 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily Administered Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide BID</td>
<td>- No dose adjustment if eGFR is ≥ 60 mL/min&lt;br&gt;- Lower dose (5 mcg BID) if eGFR 30 to 59 mL/min</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>- No dose adjustment if eGFR is &gt; 50 mL/min&lt;br&gt;- Not recommended if eGFR is less than 50 mL/min</td>
<td>Not recommended</td>
</tr>
<tr>
<td><strong>Once Weekly Administered Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albiglutide</td>
<td>- No dosage adjustment is required in patients with renal impairment.&lt;br&gt;- Caution is needed when initiating or escalating dose in patients with renal impairment.&lt;br&gt;- Monitor renal function in patients with renal impairment reporting severe gastrointestinal reactions which may worsen renal function.</td>
<td></td>
</tr>
</tbody>
</table>
### Dulaglutide
- No dosage adjustment is required in patients with renal impairment.
- Caution when initiating or escalating doses in patients with renal impairment.
- Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions.
- Should be used with caution in patients with eGFR < 30 mL/min.

### Exenatide

<table>
<thead>
<tr>
<th>Exenatide Once Weekly</th>
<th>No dose adjustment if eGFR is &gt; 50 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Use with caution when eGFR is between 30 to 50 mL/min</td>
</tr>
<tr>
<td></td>
<td>Contraindicated if eGFR &lt; 30 mL/min, including patients receiving dialysis</td>
</tr>
</tbody>
</table>

### Revisit Tom
You explain to Tom that while there is some risk of nausea with the GLP-1R agonists, nausea tends to decline with continued use over the first six to eight weeks of treatment. This makes Tom more comfortable with the adverse effects, but he is still uncertain about having to inject a medication. He thinks that this is a “drastic step” and that his diabetes isn’t that bad. He states that he thinks it would be too difficult to have to fill up a syringe and worries that he would get the dosage wrong.

### Devices for administration of GLP-1 receptor agonists
The once weekly administered GLP-1R agonists are all administered using prefilled pen devices. There are, however, some differences between the devices. For information on the liraglutide and exenatide twice daily pens, please refer to the links that follow.

- Exenatide twice daily pen
- Liraglutide pen
- Albiglutide Pen

Albiglutide is supplied as a prefilled, single-dose pen with a 29 gauge, 5 mm needle and requires reconstitution prior to administration. Albiglutide must be stored between 2°C to 8°C prior to dispensing. After dispensing, albiglutide pens can be stored in the refrigerator between 2°C to 8°C up to the expiry date or at room temperature (not to exceed 30°C) for up to 4 weeks before using. The pen should be taken out of the refrigerator and left at room temperature for 15 minutes prior to use.

Administration requires the following steps:

1. Reconstitution – the product must be used within eight hours of reconstitution.
2. Mix by slowly and gently rocking the pen side to side (no shaking).
3. Wait 15 to 30 minutes to ensure that the reconstituted solution is mixed.
4) Mix again by slowly and gently rocking the pen side to side (no shaking).
5) Inspect to ensure that the product is mixed.
6) Attach the needle to the pen.
7) Insert the needle into the skin and subcutaneously inject into the abdomen, thigh, or upper arm region by pressing the injection button.

**Dulaglutide Pen**

The dulaglutide pen is a prefilled, single dose device that does not require reconstitution or attachment of the needle. The pen has attached a small (29 gauge, 5 mm) hidden needle. The dulaglutide pen should be stored in the refrigerator at 2°C to 8°C, but can be kept at room temperature (not to exceed 30°C) for up to 14 days.

Its injection steps include:

1) Remove the cap.
2) Place the Clear Base flat and firmly against the skin of the abdomen or thigh and unlock. The upper arm may also be used.
3) Press and hold the injection button until a click is heard. Continue holding firmly against the skin until a second click is heard.
4) Remove the Pen from the skin.

**Exenatide Once Weekly Pen**

The exenatide once weekly pen is a prefilled device with a 7 mm, 23 gauge needle that requires reconstitution prior to use. It should be stored in the refrigerator between 2°C to 8°C until use. It can be stored at room temperature for up to 4 weeks before using if necessary, but must be protected from
light. Similar to the albiglutide pen, multiple steps are required for preparation and administration of the dose.

1) Take the pen out of the fridge and allow it to warm up for 15 minutes.
2) Attach the needle.
3) Reconstitute the dosage by twisting the knob.
4) Mix by firmly tapping (may need to tap 80 times or more to ensure that there are no clumps).
5) Inject immediately by removing the needle cap and inserting the needle into the skin of the abdomen, thigh or upper arm subcutaneously.
6) Press the injection button with the thumb until a click is heard. Hold for 10 seconds to make sure the full dose is injected.

Summary of Devices

Table 7 summarizes the key differences between the pen devices used to administer the once weekly GLP-1R agonists.

Table 7: Comparison of Pen Devices for the Injection of Once Weekly GLP-1R Agonists

<table>
<thead>
<tr>
<th></th>
<th>Prefilled, Single Dose Pen</th>
<th>Hidden Needle</th>
<th>Size of Needle</th>
<th>No Reconstitution Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albiglutide</td>
<td>✓</td>
<td>✗</td>
<td>29 gauge, 5mm</td>
<td>✗</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>✓</td>
<td>✓</td>
<td>29 gauge, 5mm</td>
<td>✓</td>
</tr>
<tr>
<td>Exenatide Once Weekly</td>
<td>✓</td>
<td>✗</td>
<td>23 gauge, 7mm</td>
<td>✗</td>
</tr>
</tbody>
</table>

Resistance to Treatment Intensification

It can be challenging for some patients to accept treatment with an injectable medication due to their health beliefs and other real or perceived barriers to treatment. Thus, it is important to identify and discuss any potential barriers that may exist to initiating treatment with an injectable medication. 40

Misconceptions about GLP-1R Agonists

Patients may hold the misconception that GLP-1R agonists may have similar adverse effects to insulin (e.g., hypoglycemia and weight gain) since they are both injectable medications. 40 Further, patients may feel that the need to use an injectable medication is an indication that their diabetes is getting more difficult to control. Thus, it is important to explain that diabetes is a condition that requires adjustments to therapy over time to ensure that glycemic control is adequate and that adding an injectable medication does not signify a failure on their part. 40
Fear of Injection

Patients may fear taking an injectable medication for a number of reasons. Approximately 30% to 50% of patients have fear and anxiety related to injection-associated pain. Patients may fear that they will experience considerable pain and discomfort with injection, not understanding the differences between an intramuscular injection (such as a flu shot) and a subcutaneous injection with a thinner, shorter needle.

Complexity of Administration

Patients may simply assume that administration of the GLP-1R agonists will be overly complicated and challenging, as they lack familiarity with the devices for administration, which can be simple to use. Further, once weekly administration itself can simplify a diabetes treatment regimen compared to taking a daily oral medication. While vision, dexterity issues and comorbid conditions (for example, arthritis of the hand) are considerations for older patients in particular, assessment of individual patient ability is important, as true ability is quite variable.

Strategies to approaching barriers to injectable medication use are found in Table 8.

Table 8: Strategies to Approaching Barriers to Injectable Medications

<table>
<thead>
<tr>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask patients if they have any concerns with using the GLP-1R agonists and with using an injectable medication.</td>
</tr>
<tr>
<td>Emphasize the benefits of potential weight loss and relatively low risk of hypoglycemia.</td>
</tr>
<tr>
<td>Focus on the ease of use, with administration being once weekly and without regards to meals for some options, so there may be no need to remember in advance of a meal.</td>
</tr>
<tr>
<td>Take the time to provide education on how to use the device so patients understand that the administration is simplified using a pen device and that there are different options for devices, some of which may be easier to use than others.</td>
</tr>
<tr>
<td>Offer to have the patient self-inject first dose in the pharmacy under supervision/assistance in a private counselling area.</td>
</tr>
<tr>
<td>Be sure to assess ability to use the device, including dexterity, vision, etc. to make sure the patient will not experience difficulties with administration</td>
</tr>
<tr>
<td>Set realistic treatment goals and help patients to form realistic expectations of treatment.</td>
</tr>
</tbody>
</table>

Patients may assume that administering medication by injection will be too difficult for them. Appropriate education and counselling can help to overcome this barrier.

The Patient Experience with GLP-1R Agonists

When switching to or intensifying pharmacotherapy for type 2 diabetes with injectable medications, once weekly administration may be appealing. In a survey of patients with type 2 diabetes, attitudes towards once weekly therapy were positive, particularly amongst those who were already taking injectable medications. Further, patients indicated that once weekly medication would offer greater convenience and felt that this would promote medication adherence, improve their quality of life and be less overwhelming. When asked if they would take an injectable medication once weekly if it was recommended, almost 50% agreed that they would but agreement was higher in those currently using
an injectable medication (73%) than those who did not (31.5%). Patients with a more negative impact of their diabetes on their quality of life were more willing to take an injectable medication. Thus, healthcare providers should not assume that patients will be resistant to the idea of taking a once weekly medication administered via subcutaneous injection, as attitudes may be quite positive.

In a head to head comparison of exenatide once weekly to exenatide BID, the improvement in treatment satisfaction was greater with the once weekly formulation. In this trial, while adherence was 98% for both, the once weekly formulation had higher ratings of treatment satisfaction and perceptions of convenience, flexibility, understanding and willingness to continue treatment. Further, in patients treated with exenatide once weekly, sitagliptin or pioglitazone, all groups experienced improvements in psychological well-being and improvements in treatment satisfaction, but improvements in weight-related quality of life and overall health-related quality of life were greater with exenatide once weekly than with pioglitazone. In a comparison of treatment satisfaction with albiglutide versus liraglutide, treatment satisfaction improved similarly in both groups. In summary, treatment satisfaction and quality of life are positively impacted by once weekly GLP-1R agonists.

### Treatment Adherence

Once weekly administration of the GLP-1R agonists could, in theory, create the potential for missed dosages since it might be more difficult to establish a routine due to the extended dosing interval. However, evidence from clinical trials demonstrates similar or greater levels of adherence with once weekly albiglutide and daily administered medications (**Figure 3**).

**Figure 3: Adherence to Once Weekly Albiglutide Compared with Daily Oral Antidiabetic Drugs**

Promoting Adherence to Once Weekly Medications

To help promote adherence to weekly medication, it is important to select a day of the week for administration that will work best for the individual’s schedule. As well, a consistent administration time and one that will not be impacted by other activities on that day is a good idea. It may be best to avoid a day of the week that is hectic or that is variable in the routine. For example, a week day may afford
more structure than a weekend. For medications that can be taken without regards to meals, first thing in the morning might be an appropriate time to administer the medication and an opportunity to tie this to a part of the daily routine, for example with breakfast on Monday mornings. If a dose is missed, it should be taken as soon as it is remembered, as long there is at least 72 hours (3 days) until the next dose. If there is less than 72 hours, the dose should be skipped and the next dose should be taken on the regularly scheduled day.

Reminder systems may potentially be beneficial. Patients are likely to have variable preferences and levels of experience with technology, so it is important to investigate what the individual patient would be comfortable with. For example, some patients may simply prefer to write themselves reminder on a paper calendar or in an agenda, whereas for other patients, a recurring event on a smart-phone or computer-based calendar with a programmed reminder might be a better alternative. As well, smart phone apps that allow scheduling of medication regimens and reminders are available, some examples of which include:

- My Medication Reminders
- MyMeds
- Medisafe Medication Reminder
- RxmindMe
- Care4Today™

**Revisit Tom**

After your discussion, Tom indicates that he would be open to trying a GLP-1R agonist, as he finds once weekly administration and the potential for weight loss, given his inability to meet his weight loss goals, both to be appealing. As well, you explain to Tom that the once weekly GLP-1R agonists are administered using prefilled pen devices, which can simplify the steps for injection considerably. Tom has an appointment with his physician the following week and will return to the pharmacy after that for device training and to set up a smartphone app to remind him to take his medication.

**Summary of Key Learning Points**

Treatment intensification with an injectable medication can help achieve therapeutic goals in type 2 diabetes.

GLP-1R agonists are incretin-based therapies that are administered by subcutaneous injection. GLP-1R agonists are an appealing therapeutic alternative due to their potential for A1c lowering and weight reduction in clinical trials, and relatively low risk of hypoglycemia.

Recently three GLP-1R agonists that are dosed on a once weekly basis have become available in Canada and may provide a treatment alternative to those patients who have failed to achieve blood glucose goals with oral medications and who are resistant to taking a daily administered injectable medication.

While GLP-1R agonists require subcutaneous administration, the ease of administration with pen devices on a once weekly basis may help to overcome resistance to intensifying treatment with this alternative.
It is important to have an open dialogue with patients about any fears or concerns that they may have about injectable medications and work with patients to alleviate these issues, to help promote adherence and overcome treatment barriers.

Post-Test

1. Albiglutide, dulaglutide and exenatide
   a) Lower blood glucose by antagonizing the actions of GLP-1 at its receptor
   b) May cause weight loss by promoting a feeling of satiety
   c) Frequently cause hypoglycemia as an adverse effect
   d) A and B only
   e) All of the above

2. Albiglutide
   a) Is a human-based GLP-1R agonist
   b) Was superior to placebo, sitagliptin, and glimepiride in reducing A1c in clinical trials
   c) Was noninferior to insulin lispro and insulin glargine in reducing A1c in clinical trials
   d) A and B only
   e) All of the above

3. Dulaglutide
   a) Is an exendin-4 based GLP-1R agonist
   b) Is administered subcutaneously, on a once weekly basis using a pen device.
   c) Is fused to carrier molecule to extend its duration of action
   d) B and C only
   e) All of the above

4. Exenatide once weekly
   a) Is administered as a once weekly, intramuscular depot injection
   b) Is structurally based on human-based GLP, but achieves its extended duration by the additional of a fatty acid side chain
   c) Has a higher incidence of injection site reactions than exenatide twice daily.
   d) Does not require reconstitution prior to administration

5. Potential benefits of GLP-1R agonists include
   a) A relatively low risk of hypoglycemia
   b) Potential for weight loss
   c) Once weekly administration for some products (albiglutide, dulaglutide and exenatide once weekly)
   d) All of the above

6. Which of the follow is correct?
   a) When glucose is taken orally, the amount of insulin secreted in response is less than if the same glucose load was taken intravenously.
b) GLP-1 receptors are found in the pancreas, lung, heart, blood vessels, gastrointestinal tract, kidney, breast and central nervous system.
c) In the gastrointestinal tract, GLP-1 increases motility, which speeds gastric emptying.
d) All of the above

7. Nausea with the GLP-1R agonists
   a) Generally resolves within 6 to 8 weeks of treatment
   b) Tends to resolve more slowly with exenatide twice daily than with once weekly GLP-1R agonists
   c) May be related to reduced gastric emptying
   d) All of the above are correct

8. Which of the following is correct about the GLP-1R agonists?
   a) The risk of hypoglycemia is decreased when added to sulfonylurea or basal insulin therapy.
   b) The albiglutide and liraglutide are administered once weekly.
   c) Injection site reactions have been more frequently reported with albiglutide and exenatide once weekly than with other GLP-1R agonists.
   d) A and C are correct
   e) All of the above are correct

9. In clinical trials
   a) Dulaglutide has been shown to be superior to placebo, metformin, sitagliptin, exenatide, and insulin glargine in reducing A1c.
   b) Exenatide once weekly has been shown to be superior to liraglutide in reducing A1c
   c) Albiglutide was superior to placebo, sitagliptin, and glimepiride in reducing A1c
   d) A and C are correct
   e) All of the above

10. For patients who are resistant to initiating treatment with an injectable medication, it may be beneficial to
   a) Identify any concerns they have and work with the patient to resolve these issues
   b) Stress the benefits of the GLP-1R agonists, such as weight loss and low risk of hypoglycemia
   c) Provide training on the injection device and have the patient administer their first dose in the pharmacy to help build confidence.
   d) All of the above

Resources
Health Care Provider Resources
Canadian Diabetes Association Guidelines and 2015 Pharmacotherapy Update

Clinical Information

HARMONY Studies (Albiglutide)

- HARMONY-2: http://www.easdvirtualmeeting.org/resources/3898
- HARMONY-7: http://www.thelancet.com/journals/landia/article/PIIS2213-8587(13)70214-6/abstract
- HARMONY-8: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4049886/

AWARD Studies (Dulaglutide)

- AWARD-1: http://care.diabetesjournals.org/content/37/8/2159.full
- AWARD-3: http://care.diabetesjournals.org/content/37/8/2168.full.pdf
- AWARD-4: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)60936-9/abstract

DURATION Studies (Exenatide Once Weekly)

- DURATION 2: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3123706/
- DURATION 6: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)61267-7/abstract

Patient Resources

Instructions for Administration

Albiglutide Pen: http://www.tanzeum.com/how-to-use.html


Exenatide Once Weekly Pen: http://www.azpicentral.com/bydureo/ifu_bydureon.pdf#page=1
Lifestyle Management


SmartPhone Apps

My Medication Reminders
MyMeds
Medisafe Medication Reminder
RxmindMe

References


27. Stewart MHP, Yang F, et al. 52-week efficacy of albiglutide vs placebo and vs pioglitazone in triple therapy (background metformin and glimepiride) in patients with type 2 diabetes:


32. Giorgino F, Benroubi M, Sun J, Zimmermann AG, Pechtner V. Efficacy and safety of once-weekly dulaglutide vs. insulin glargine in combination with metformin and glimepiride in type 2 diabetes patients (AWARD-2). Published online before print.Diabetes Care June 18, 2015.


43. Best JH, Rubin RR, Li Y, et al. Weight-related quality of life, health utility, psychological well-being, and satisfaction with exenatide once weekly compared with sitagliptin or pioglitazone