

# Glucagon-like peptide-1 analogues – a practical guide to initiation

Ralph Audehm and Laura Dean

**Glucagon-like peptide-1 (GLP-1) analogues are one of the more recent additions to the type 2 diabetes armamentarium and work by mimicking the incretin system to lower glucose and increase insulin. The drug class also exerts associated non-glycaemic advantages, such as weight loss. The first GLP-1 analogue was approved for use in Australia in 2007 and has been subsidised by the Pharmaceutical Benefits Scheme since 2008, yet its use remains relatively low. This article discusses the mode of action of GLP-1 analogues, their use in Australia and how to use and initiate GLP-1 analogues in people with type 2 diabetes, using case studies.**

Glucagon-like peptide-1 (GLP-1) is a hormone released by the gut when sensory receptors in the small intestine detect dietary glucose and other nutrients. GLP-1 forms part of the “incretin effect” – the increased secretion of insulin when the same amount of glucose is ingested orally compared to when it is administered intravenously (Willard and Sloop, 2012). The incretin system potentiates glucose-induced insulin secretion and may be responsible for up to 70% of post-prandial insulin secretion (Holst et al, 2009). GLP-1 is also known to be involved in the inhibition of glucagon release (thus decreasing hepatic production of glucose and fasting blood glucose levels), delayed gastric emptying (thus decreasing post-prandial blood glucose levels) and the suppression of appetite, which, in theory, leads to decreased calorie intake (Gupta, 2013). The roles of GLP-1 make it an attractive target for drug development, especially for the management of type 2 diabetes where the incretin effect is severely reduced or absent in patients (Holst et al, 2009). In addition, the half-life of endogenous GLP-1 is less than 2 minutes, so creating GLP-1 analogues that can be active for longer is of great benefit.

Dipeptidyl peptidase-4 (DPP-4), an endogenous enzyme also involved in the

incretin system, rapidly inactivates GLP-1, leading to its short half-life (Willard and Sloop, 2012). It is now possible to artificially prolong the half-life of GLP-1 and its effect by using DPP-4 inhibitors, or “gliptins”. The first DPP-4 inhibitor to be approved by the US Food and Drug Administration was saxagliptin in 2006. The drug class is well tolerated by users, is weight neutral and has a low risk of hypoglycaemia unless used in combination with medications with a risk of hypoglycaemia, such as sulfonylureas (Prasad-Reddy and Isaacs, 2015). They are administered in tablet form and are available in a combined tablet with metformin. Studies have shown they can reduce HbA<sub>1c</sub> by 4.4–7.7 mmol/mol (0.4–0.7%; Brunton, 2014).

Around the same time, GLP-1 analogues were developed to be more resistant to the actions of DPP-4 inhibitors and with a longer half-life than endogenous GLP-1. The advantages and disadvantages of using GLP-1 analogues are presented in *Table 1*. GLP-1 analogues have been shown to reduce HbA<sub>1c</sub> by around 10.9 mmol/mol (1%; Kenkre et al, 2013) and they can be combined with insulin as GLP-1 analogues are weight negative and insulin is weight positive (Cohen et al, 2013). Devices that contain both basal insulin and a GLP-1 analogue in a single injection have been

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## Article points

1. The incretin system is used to develop pharmacological therapies for type 2 diabetes.
2. The incretin mimetics, glucagon-like peptide-1 (GLP-1) analogues, represent a useful and effective tool in the management of type 2 diabetes
3. GLP-1 analogues are an under utilised resource in the type 2 diabetes armamentarium.

## Key words

- Administration
- Glucagon-like peptide-1 analogues
- Glucose-lowering medication
- Incretin system

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approved in Europe and USA (insulin degludec/liraglutide; Greig and Scott, 2015).  
 Table 2 gives an overview of GLP-1 analogues

that are approved by the Therapeutic Goods Administration (TGA) for use in Australia: exenatide, exenatide-modified release, liraglutide

**Table 1. Advantages and disadvantages of glucagon-like peptide-1 (GLP-1) analogues.**

Advantages	Disadvantages
Significant weight loss: 3–4 kg on an intention to treat analysis (Robinson et al, 2013).	Gastrointestinal effects (e.g. nausea and diarrhoea): 5–10% of people will stop a GLP-1 analogue due to nausea (Meier, 2012).
Decreased post-prandial excursions.	Pancreatitis: There was an early signal suggesting that GLP-1 analogues may increase the risk of pancreatitis. Follow-up studies have shown that the risk for pancreatitis is no greater than the background incidence of pancreatitis in people with type 2 diabetes (Forsmark, 2016).
Glucose-dependent manner: GLP-1 analogues do not cause hypoglycaemia unless used with other medications, such as sulfonylureas or insulin.	Delivery of the dose: GLP-1 analogues must be injected.
Liraglutide has recently been shown to reduce mortality in people with type 2 diabetes (Marso et al, 2016).	Renal insufficiency: GLP-1 analogues should not be used if eGFR <30 mL/min/1.73 m <sup>2</sup> .
	Expense: While exenatide is subsidised by the PBS under certain conditions, liraglutide is not, and lixisenatide is not available in Australia.

eGFR=estimated glomerular filtration rate; PBS= Pharmaceutical Benefits Scheme.

**Table 2. Overview of glucagon-like peptide-1 (GLP-1) analogues available in Australia.**

GLP-1 analogue (tradename; manufacturer)	Dosing	Subcutaneous injection technique	Storage	Funding
Exenatide (Byetta®; Eli Lilly)	5 or 10 µg twice daily up to 1 hour before breakfast or dinner, at least 6 hours apart if administered before lunch and dinner. Not to be taken after food.	4–6 mm needle (the same needles as for insulin). The injection technique and sites are the same as for insulin.	In the fridge (2–8°C) Pen in use may be kept at room temperature for 1 month. Re-cap to protect from light.	Exenatide is available on the PBS as a twice-daily injection. The twice-daily injection is PBS-subsidised for dual therapy with metformin or a sulfonylurea, or triple therapy with metformin, a sulfonylurea and insulin.
Exenatide-modified release (Bydureon®; Eli Lilly)	2 mg/mL once weekly, on the same day.	Contains needles in the kit. The injection technique and injections sites are the same as for insulin. Exenatide-modified release has to be shaken robustly once the diluent has been added to suspend the drug uniformly – this can be done by tapping at least 80 times against your palm, and rotating the pen every 10 taps, until the mixture is uniformly cloudy with no clumps. Injection must occur immediately after mixing or clumps may form. Tips on use of the pen and injection technique can be found at <a href="https://www.youtube.com/watch?v=9BnXaBIF3kw">https://www.youtube.com/watch?v=9BnXaBIF3kw</a> (accessed 28.10.16).	In the fridge (2–8°C). Pen (unmixed) may be kept at room temperature for 1 month. Should be at room temp for 15 minutes before mixing to improve solubility. Use immediately after mixing.	Exenatide-modified release is a weekly injection and is PBS listed for dual and triple therapy but not with insulin.
Liraglutide (Victoza®; Novo Nordisk)	0.6–1.8 mg, once daily.	4–6 mm needle (the same needles as for insulin). The injection technique and sites are the same as for insulin.	In the fridge (2–8°C) Pen in use may be kept at room temperature for one month. Re-cap to protect from light.	Liraglutide is not listed on the PBS but is available as a daily injection and is approved for use in type 2 diabetes. Costs are around \$159.50 for the two-pen pack (1 month's supply at 1.2 mg dose) and \$236.84 for the three-pen pack (1 month's supply at 1.8 mg dose).*

\* Liraglutide is also approved by the Therapeutic Goods Administration for weight loss at 3 mg under the tradename Saxenda®.  
 PBS=Pharmaceutical Benefits Scheme.

and lixisenatide. Lixisenatide is not currently being supplied in Australia.

## How to initiate GLP-1 analogues

### Exenatide

Exenatide (Byetta<sup>®</sup>) is available in two dose forms, 5 µg and 10 µg. Patients should initiate with 5 µg twice daily. The dose should be injected within the 60 minutes before their breakfast and evening meal. Exenatide can be administered before the lunch and evening meal, as long as the injections are at least 6 hours apart. The dosage can be increased to 10 µg twice a day after 1 month at 5 µg if tolerated.

### Exenatide-modified release

Exenatide-modified release (Bydureon<sup>®</sup>) is a long-acting form of exenatide. It is available in a 2 mg/mL dose and it is administered once a week on the same day. There is no dose titration required and it can be given at any time of the day without reference to meals. The formulation uses microspheres to provide the modified-release properties, which results in a delayed onset of action, such that it may take 2 weeks for the exenatide to begin being released, and up to 7 weeks for complete release (Cai et al, 2013). To manage expectations, people using once-weekly exenatide should be made aware of this delay.

If a patient wishes to change the day on which they administer the injection, they may do so as long as there is more than one clear day between the injections. Similarly if a patient forgets to inject the exenatide-modified release, they may administer it as soon as they remember. However, if there are only one or two days until the next scheduled dose, they should wait until the scheduled day to take their dose (Eli Lilly Australia Pty, 2013).

It is important to be aware that the microspheres in long-acting exenatide can lead to an inflammatory reaction and “nodules” or subcutaneous lumps developing at the injection site, which are usually asymptomatic and resolve over 4–8 weeks (DeYoung et al, 2011).

### Liraglutide

Liraglutide (Victoza<sup>®</sup>) is available as a single pen device containing three different dosing options: 0.6 mg, 1.2 mg and 1.8 mg. The starting dose is 0.6 mg daily, which can be increased to 1.2 mg after at least 1 week and, if tolerated, can be increased to 1.8 mg to achieve maximum efficacy. The dose is given independently of meals but should be given around the same time each day.

If patients are on insulin or a sulfonylurea, it is useful to ask them to monitor their glucose levels four times per day for the first 3–4 days to identify any risk of hypoglycaemia. If the HbA<sub>1c</sub> for a patient is <64 mmol/mol (8%), consider reducing the insulin or sulfonylurea dose until their glycaemic pattern stabilises.

Liraglutide at a higher dose is also marketed under the name Saxenda<sup>®</sup>. Saxenda was registered with the TGA on 24 December 2015 as a weight-loss treatment for adults with a BMI ≥30 kg/m<sup>2</sup> (obese), or with a BMI ≥27 kg/m<sup>2</sup> but less than 30 kg/m<sup>2</sup> if they have at least one weight-related comorbidity (e.g. dysglycaemia, hypertension, dyslipidaemia or obstructive sleep apnoea). The starting dose is 0.6 mg, which can be titrated to a maximum maintenance dose of Saxenda of 3 mg daily.

### Case studies

The following case studies illustrate how to initiate GLP-1 analogues in people with type 2 diabetes.

#### Case 1

Mr GL is a 49-year-old person who was diagnosed with type 2 diabetes a year ago and currently has a BMI of 32 kg/m<sup>2</sup>. He is currently taking metformin 1000 mg daily (he developed bloating at the higher dose), but is on no other medication. He has engaged in some lifestyle changes but his HbA<sub>1c</sub> and weight have slowly increased – his current HbA<sub>1c</sub> is 54 mmol/mol (7.1%). He feels his medication is no longer working, and he is concerned about his increasing weight. Sulfonylureas were an unsuitable addition to his medication as he was a part-time taxi driver, and the risk of having a hypoglycaemic event was unacceptable for his licence.

*“If a patient wishes to change the day on which they administer their long-acting glucagon-like peptide-1 analogue, they may do so as long as there is more than one clear day between the injections.”*

***“It is beneficial to warn all people using glucagon-like peptide-1 analogues to expect nausea, especially in the first 2–3 days after initiation.”***

After discussing options for treatment intensification, he elected to trial exenatide. Exenatide 5 µg was commenced twice daily and increased to 10 µg after a month. He tolerated the injection very well and found the injections easy to administer. Six months later, Mr GL had achieved a weight loss of 4 kg and his HbA<sub>1c</sub> was 40 mmol/mol (5.8%).

### Case 2

Ms PI is a 54-year-old lady with a HbA<sub>1c</sub> 88 mol/mol (10.2%). Her blood pressure (BP) is 140/85 mmHg and she has a BMI of 31 kg/m<sup>2</sup>. She has no nephropathy and her estimated glomerular filtration rate (eGFR) is >90 mL/min/1.73 m<sup>2</sup>. She has retinopathy and has had laser therapy treatment in the past. She is currently on a combined tablet of metformin and DPP-4 inhibitor (metformin 1000 g/linagliptin 2.5 mg) twice daily, but she has an erratic lifestyle and has difficulties remembering her medications. After discussing her options, including insulin, she elected to start exenatide-modified release, feeling that a weekly injection would be easier to manage. She understood that she would need insulin in the future but the GLP-1 analogue would help reduce the amount of weight she would gain with insulin. The metformin/DPP-4 inhibitor combination was stopped and the exenatide-modified release commenced with metformin XR 1000 mg twice daily. The initial injection was supervised with the practice nurse and Ms PI felt confident with the injections.

At 3 weeks, she had lost 2.5 kg and her daily blood glucose levels were now in the low teens. Ms PI has had minimal side effects as a result of the change in drug regimen. She was happy with the weight loss she has achieved and improved blood glucose levels and is now more engaged with the practice and attending appointments more regularly, offering the opportunity for ongoing treatment intensification if required.

### Case 3

RA is a 60-year-old male. He is on insulin glargine 48 units per day, metformin 2000 mg daily and gliclazide MR 120 mg daily, as well as anti-hypertensives and a statin. His

HbA<sub>1c</sub> is 66 mmol/mol (8.2%). He has minimal non-proliferative retinopathy and a marginally elevated albumin–creatinine ratio (7 mg/mmol). His BP at his most recent appointment was 138/70 mmHg and his BMI was 35 kg/m<sup>2</sup>. On discussion with the clinician, self-blood glucose monitoring results showed large post-prandial elevations: these were highest after dinner (around 12–13 mmol/L) but also high at lunch. His fasting blood glucose measurements were around 7 mmol/L. Exenatide was commenced at 5 µg bd, prior to breakfast and dinner. The device and the injection technique were demonstrated at an appointment later in the day so that he could then go home and have his evening meal. He was told to monitor his blood glucose levels four times a day and to carry jellybeans or another quick-acting glucose source with him at all times.

At review 1 week later, his fasting blood glucose had dropped, and during the preceding week, were often below 5 mmol/L but not below 4 mmol/L. He was comfortable with administering the injections and elected to reduce his gliclazide to minimise his risk of hypoglycaemia. Another review was organised for a week's time. If exenatide 5 µg dose continues to be well tolerated, after 1 month, the exenatide dose will be increased to 10 µg bd.

### How to manage the side effects of GLP-1 analogues

The most common side effects reported by people using GLP-1 analogues are nausea and vomiting (Garber, 2011). Therefore, it is beneficial to warn all patients to expect nausea, especially in the first 2–3 days. The nausea will usually settle, but to diminish these effects you may suggest that they eat smaller meals or snacks in the interim. Anti-emetics can be used in the short term to help patients overcome this period of nausea. Exenatide-modified release and liraglutide have lower rates of nausea than exenatide (Garber, 2011).

### Summary

The GLP-1 analogue drug class offers a drug regimen for people with type 2 diabetes that is well tolerated by users, weight neutral and

with a low risk of hypoglycaemia. It is straightforward to initiate and titrate, but it is currently underutilised. In 2015, there were just over 200 000 scripts for exenatide compared to more than 2 million scripts for a DPP-4 inhibitor (The Pharmaceutical Benefits Scheme, 2015). GLP-1 analogues are an excellent addition to our armamentarium. ■

### Declaration

Ralph Audehm has received monies from Sanofi, AstraZeneca, NovoNordisk, Novartis and Lilly for consultancy work.

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**“As the most common side effects reported by people using glucagon-like peptide-1 analogues are nausea and vomiting, it is beneficial to warn all patients to expect nausea, especially in the first 2–3 days of use.”**