

GLP-1 receptor agonists

Today (2019-Jan-7) in Canada 4 agents in the GLP-1 receptor agonist (RA) class are marketed:

- liraglutide** (Victoza, Saxenda), usual maintenance dose 1.8 mg daily (\$7/day)
- semaglutide** (Ozempic), usual maintenance dose 1.0 mg weekly (\$7/day)
- dulaglutide** (Trulicity), usual maintenance dose 1.5 mg weekly (\$7/day)
- lixisenatide** (Adlyxine), usual maintenance dose 10 ug daily (\$5/day)

All currently marketed GLP-1 RAs are injectable & all are effective in lowering sugar and weight. An oral version of semaglutide is under investigation and has been shown to be highly effective.

The final maintenance dose of GLP-1 RAs is determined by the presence or absence of GI side-effects, response to therapy (and cost). 30% of patients have strong responses both in A1c- and weight-lowering. 50% of patients have relatively modest responses to therapy. 10-15% of patients are intolerant of GLP-1 RAs because of nausea & vomiting.

The recommended starting dose of GLP-1 RAs is $\frac{1}{4}$ to $\frac{1}{3}$ usual maintenance dose (see above). Dose increases can be considered after 1-2 weeks. If mild nausea occurs try maintaining dose for longer. If severe nausea or vomiting hold for 1 week and try $\frac{1}{2}$ the dose associated with N&V.

The GLP-1 RA effect on satiety is achieved through two mechanisms: central appetite suppression & delayed gastric emptying (patients feel full after meals). Blood glucose lowering is achieved both through weight loss (with increased insulin sensitivity) & through the independent effect of enhanced meal-related insulin secretion (the "incretin" effect).

In head-to-head studies semaglutide is the most efficacious of the GLP-1 RA class for both glucose-lowering & weight reduction. If semaglutide is prescribed using the 4 mg pen, a dose of 0.5 mg weekly costs \$3.50/day. This is the recommended maintenance dose for individuals with a financial barrier.

When used in individuals with Type 2 diabetes with prior CV events, liraglutide, semaglutide & dulaglutide are associated with decreased mortality or MACE.

Liraglutide in combination with insulin degludec (Xultophy, maximal dose of liraglutide 1.8 mg is achieved with 50 U degludec) & lixisenatide in combination with insulin glargine (Soliqua, 10 ug with 60 U) are useful agents whose market is yet to be determined.