



**Drug information question:** For people with type 2 diabetes, how does the oral daily formulation of semaglutide (Rybelsus®) compare with the subcutaneous weekly formulation (Ozempic®)?

**Conclusion: Both formulations of semaglutide lower HbA1c and body weight and have demonstrated cardiovascular safety when compared to placebo. As an alternative to the subcutaneous formulation, the oral formulation is similar in cost but involves complex administration instructions which may limit its suitability.**

The BC Provincial Academic Detailing (PAD) Service's 2021-2022 [Type 2 Diabetes Focused Update: SGLT2 inhibitors and GLP1 Agonists](#) addresses:

- Changes to available evidence and clinical practice guidelines, informing medication choices beyond HbA1c lowering.
- Clinical considerations which support treatment decisions including doses, adverse events, dosage forms, cost and coverage.

Several injectable GLP1 agonist medications are marketed in Canada, however, only semaglutide is available both as an [injectable subcutaneous formulation](#) (Ozempic®) and an [oral tablet formulation](#) (Rybelsus®).<sup>1,2</sup> It is difficult to administer peptide-based medications, such as GLP1 agonists, orally as they are degraded by enzymes in the gastric environment.<sup>3</sup> To address this, each semaglutide tablet is co-formulated with 300 mg of an excipient, SNAC (salcaprozate sodium), which buffers against the acidity of the stomach near the tablet and facilitates the drug's absorption across the gastric epithelium.<sup>3</sup> Pharmacokinetic studies indicate that excess SNAC or water in the stomach reduces semaglutide absorption and the presence of food can prevent absorption entirely.<sup>3</sup> Successful administration involves several steps to ensure oral bioavailability, which is low at approximately 1%.<sup>2</sup>

- Take on an empty stomach at least 30 minutes before food, beverages or any other oral medication.
- Take with water (but not more than 120 mL) and swallow the tablet whole (do not split, crush or chew).
- Do not take more than one tablet per day: do not combine two 7 mg tablets to achieve a 14 mg dose, as doubling the amount of SNAC per dose may reduce semaglutide absorption.

In trials enrolling people with type 2 diabetes plus cardiovascular disease or multiple cardiovascular risk factors, GLP1 agonists reduce the risk of adverse cardiovascular events.<sup>4</sup> The oral and subcutaneous formulations of semaglutide have not been compared directly<sup>5</sup> but both seem to have cardiovascular benefits consistent with the class as a whole.<sup>4</sup> Neither the oral or subcutaneous semaglutide cardiovascular trials were prospectively designed to show superiority however and have not yet been granted indications by Health Canada beyond HbA1c lowering.<sup>1,2,5-7</sup> Ongoing trials are anticipated to provide additional information on all-cause mortality, cardiovascular and kidney outcomes, and the risk of retinopathy.<sup>8</sup>

Both formulations reduce HbA1c and body weight compared with placebo.<sup>9,10</sup>

- Reduction in HbA1c when added to metformin: subcutaneous ~1.3%, oral ~0.9%.
- Reduction in body weight: subcutaneous ~3.8 kg, oral ~2.4 kg.

Both formulations require dose titration at initiation which is intended to minimize gastrointestinal adverse events, the most common reason that people discontinue semaglutide.<sup>1,2,6,7</sup>

In British Columbia, subcutaneous semaglutide costs approximately \$2,900 per year and oral semaglutide costs approximately \$2,800 per year, excluding markup and professional fees.<sup>8</sup> Subcutaneous semaglutide is a [Limited Coverage Drug](#), accessible through BC PharmaCare.

<sup>1</sup>Health Canada Semaglutide Subcutaneous (Ozempic); <sup>2</sup>Health Canada Semaglutide Oral (Rybelsus); <sup>3</sup>US FDA 2019 Rybelsus Pharmacology Review;

<sup>4</sup>SATTAR Lancet Diabetes Endocrinol 2021 (PMID: 34425083); <sup>5</sup>CADTH 2021 Can J Health Tech 2021 Semaglutide Oral (Rybelsus); <sup>6</sup>SUSTAIN 6 New Engl J Med 2016 (PMID: 27633186); <sup>7</sup>PIONEER 6 N Engl J Med 2019 (PMID: 31185157); <sup>8</sup>BC PAD Service; <sup>9</sup>TSAPAS Ann Int Med 2020 (PMID: 32598218);

<sup>10</sup>TSAPAS Diabetes Obes Metab 2021 (PMID: 34047443)