News

Semaglutide's slimming properties shifts the scales towards scarcity and shams

Ilze Vermaak

Department of Pharmaceutical Sciences, Faculty of Science, Tshwane University of Technology, Private Bag X680, Pretoria 0001, South Africa

Corresponding author, email: vermaaki@tut.ac.za

Abstract

Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), has gained attention for its complementary benefits of effective glycaemic control and body weight reduction. However, a concerning trend has emerged as semaglutide, particularly Ozempic®, intended for the treatment of type 2 diabetes, is prescribed off-label for its weight loss properties, leading to a worldwide stock shortage and complicating the treatment of diabetes patients stabilised on this medicine. The surge in demand, fuelled by social media coverage and celebrity endorsements, has prompted the production of counterfeit 'Ozempic' products, some containing insulin, posing serious health risks. Health regulatory authorities globally are actively monitoring and warning against counterfeit products, emphasising the importance of using authentic medicines obtained through legal medicine supply chains, prescribed by healthcare professionals. SAHPRA has urged the public to use only registered Ozempic® products, highlighting the health risks associated with unregistered and falsified medicines, and to report any suspicious products.

Keywords: GLP-1 RA; glucagon-like peptide-1 receptor agonist; Ozempic®; semaglutide; type 2 diabetes mellitus

Introduction

In South Africa, the challenge of diabetes and obesity poses significant health concerns and high costs to the healthcare system.[1] Semaglutide was introduced as an effective treatment for type 2 diabetes, offering the dual solution of glycaemic control and weight loss.[2] In South Africa, semaglutide is marketed under the trade name Ozempic®.[3] Due to the observed efficacy of Ozempic® in promoting weight loss, it is being prescribed off-label for this property, although it is indicated only for the treatment of type 2 diabetes. This unintended usage has led to a shortage, exacerbating the difficulties faced by those in need of diabetes treatment.[4] Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA), that exerts its action by selectively binding to and activating the GLP-1 receptor. The GLP-1 receptor is the target for endogenous GLP-1, a physiological hormone that has various actions on glucose, mediated by GLP-1 receptors. Semaglutide lowers blood glucose levels by stimulating insulin secretion and reducing glucagon secretion in a glucose-dependent manner. Therefore, in the presence of elevated blood glucose, insulin secretion is increased while glucagon secretion is suppressed. Additionally, the mechanism of blood glucose reduction includes a slight delay in gastric emptying during the early postprandial phase. Semaglutide is also indicated for patients with type 2 diabetes in combination with established cardiovascular disease to reduce the risk of major adverse cardiovascular events.[3]

Products and indications

Semaglutide (Ozempic®) is not the only GLP-1 RA registered in South Africa. Exenatide (Byetta® and Bydureon BCise®) and dulaglutide (Trulicity®) are also indicated in the treatment of type 2 diabetes mellitus as add-on therapy together with other glucose-lowering medicines, diet and exercise, if adequate glycaemic control is not achieved. Byetta® is injected subcutaneously twice daily while Bydureon BCise® and Trulicity® are injected once weekly, like Ozempic®. Exenatide and dulaglutide does not cause significant weight loss. Victoza® (liraglutide) is injected daily and is registered for the treatment of type 2 diabetes. Saxenda®, also containing the active pharmaceutical ingredient liraglutide and injected once daily, is the only GLP-1 receptor agonist registered in South Africa specifically for weight loss. For weight loss, the dose administered is significantly higher than the dose used to treat diabetes, in the case of semaglutide and liraglutide.[4]

Efficacy and safety

The efficacy of semaglutide in the treatment of type 2 diabetes mellitus has been established and the added benefit of weight loss has been proven.[2] Hu et al. recently reviewed the efficacy and tolerability of subcutaneous semaglutide compared to placebo or other antidiabetic agents. In this review, 17 clinical trials enrolling a total of 14 940 type 2 diabetes patients were included. It was shown that semaglutide significantly reduced blood glucose, body weight and systolic blood pressure, thereby exerting an indirect cardiovascular protective effect. Semaglutide showed beneficial effects on glycosylated haemoglobin A1C (HbA1C) control. The most common treatment-related side effects were mild to moderate gastrointestinal disturbances, similar to those experienced when using other GLP-1 RAs. These effects were dose-dependent and included mainly nausea, diarrhoea and vomiting. The

Active pharmaceutical ingredient	Trade name	Registered Indications
Semaglutide	Ozempic®	Treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise: • as monotherapy when metformin is considered inappropriate due to intolerance or contraindications. • as combination therapy with oral anti-diabetic medici=nes (metformin, thiazoledinediones, sulphonylurea), basal insulin with or without metformin and pre-mix insulin. • to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease.[3]
Dulaglutide	Trulicity®	• An adjunct to diet and exercise to improve glycaemic control in adults and paediatric patients 10 years of age and older with type 2 diabetes mellitus. • To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors.[5]
Exenatide	Byetta®	• Add-on therapy for adult patients with type 2 diabetes mellitus inadequately controlled by lifestyle modification and other oral antidiabetic therapy. • Add-on therapy to basal insulin with or without other oral antidiabetic therapy in adults who have not achieved adequate glycaemic control with oral antidiabetic agents.[6]
	Bydureon BCise®	Adults 18 years and older with type 2 diabetes mellitus to improve glycaemic control in combination with other glucose-lowering medicinal products including basal insulin, when the therapy in use, together with diet and exercise, does not provide adequate glycaemic control.[7]
Liraglutide	Victoza®	An adjunct to diet and exercise to achieve glycaemic control in patients with type 2 diabetes mellitus. Indicated for once-daily administration as: • monotherapy • combination therapy with one or more oral antidiabetic medicines (metformin, sulphonylureas, sodium-glucose cotransporter 2 inhibitor (SGLT2i) or a thiazolidinedione) when previous therapy does not provide adequate glycaemic control. • combination therapy with insulin in patients not achieving adequate glycaemic control with Victoza® and metformin.[8]
	Saxenda®	An adjunct to a reduced-calorie diet and increased physical activity for medically supervised chronic weight management programme in adult patients with an initial Body Mass Index (BMI) of: • ≥ 30 kg/m² (obese), or • ≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight related comorbidity such as dysglycaemia (pre-diabetes and type 2 diabetes mellitus), hypertension, dyslipidaemia, or obstructive sleep apnoea. Adolescents: Saxenda® can be used as an adjunct to a healthy nutrition and physical activity counselling for weight management in adolescent patients from the age of 12 years and above with: • body weight above 60 kg and • obesity (BMI corresponding to ≥30 kg/m² for adults by international cut-off points)*.[9]

gastrointestinal effects of this class of medicines may be explained by its binding to GLP-1 receptors in the gastrointestinal tract which slows gastric emptying. In addition, the activation of central GLP-1 receptors may exacerbate anorexia and satiety, resulting in gastrointestinal discomfort. This review noted no statistically significant differences in the incidence of increased risk of acute pancreatitis and diabetic retinopathy when comparing semaglutide to other antidiabetic agents.[2] The use of Ozempic® (semaglutide) carries a risk of thyroid C-Cell tumours and it is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) and in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2). Instances of medullary thyroid carcinoma (MTC) have been documented in individuals undergoing treatment with liraglutide during the post-marketing period. However, the information is insufficient to confirm or rule out a causal connection between the use of GLP-1 receptor agonists and MTC in humans. Consequently, patients should be counselled regarding recognising the symptoms of thyroid tumours; for example, persistent hoarseness, dysphagia, dyspnoea or a mass in the neck.[3]

Scarcity and scams

Ozempic® was approved by the Food and Drug Administration (FDA) in the USA for the treatment of adults with type 2 diabetes in December 2017. In January 2020, it was approved for cardiovascular risk reduction in adults with type 2 diabetes with known heart disease. More recently, in March 2022, the FDA approved a higher dose Ozempic® (2 mg) providing increased glycaemic control in adults with type 2 diabetes.[10] Ozempic® was approved in the treatment of type 2 diabetes in the United Kingdom in 2019[11] and in South Africa in July 2020.[3] Due to the soar in demand for Ozempic®, stocks have dwindled globally. This shortage is fuelled by wide social media coverage such as the use of Ozempic® by celebrities.[12] Despite unabated production, 24 hours per day, 7 days per week, Novo Nordisk expects shortages to last until at least mid-2024.[11] Reuters highlighted some of the shortage issues in the UK on 18 November, describing a real-life scenario where an affluent executive battling weight gain had a nine-month supply of Ozempic® in stock while a type 2 diabetic retiree who is relying on National Health Insurance (NHI) is uncertain when she will get her next dose. Despite a directive by the British government to prescribe semaglutide only to treat diabetes and not for weight loss, regulatory

bodies do not have the power to prohibit physicians from prescribing medicines that they believe can help their patient, even in times of shortages.[11] This is also the situation in the USA and South Africa.

The Medicines and Healthcare products Regulatory Agency (MHRA) released a drug safety update on 23 November 2023 that potentially harmful, falsified Ozempic® and Saxenda® products have been seized in the UK. No falsified Ozempic® pens were seized before January 2023, while up to October 2023, 369 potentially falsified pens were seized. They emphasised that patients should be reminded that medicines purchased outside of the legal supply chain, may not contain the ingredients stated on the label. Relabelled Ozempic® and Saxenda® pens which contained insulin was seized in the UK. Some patients had to be hospitalised and showed serious side effects like hypoglycaemic shock. Healthcare professionals and the public were advised to remain vigilant for symptoms indicating hypoclycaemia such as dizziness, sweating and blurred vision and to quarantine and retain suspect products for testing.[13]

NBC News reported on 28 December 2023 that the FDA seized thousands of counterfeit units of Ozempic® and was working with Novo Nordisk to determine the content. The European Medicines Agency (EMA) reported that counterfeit Ozempic® products were identified at wholesalers in the UK and European Union. These fake Ozempic® pens were labelled in German. German authorities stated in November that counterfeit Ozempic® products seized contained insulin. The Austrian Federal Office for Safety in Healthcare reported that several people were hospitalised after using fake products resulting in hypoglycaemia and seizures.[14] The Partnership for Safe Medicines, which tracks counterfeit injectable diabetes and weight loss GLP-1 agonists globally, noted that counterfeit products have been discovered in Australia, Austria, Azerbaijan, Belgium, Egypt, Germany, Iraq, Ireland, Jordan, Lebanon, Nigeria, Russia, South Africa, Turkey, United Kingdom and Uzbekistan. The website also contains tips on how to recognise authentic and counterfeit Ozempic® pens and images of black market semaglutide purchased online.[15]

The South African Health Products Regulatory Authority (SAHPRA) urged the public in a media release on 11 December 2023 to ensure that they only use registered Ozempic® products as they have been made aware of falsified 'Ozempic' being sold on the market and online. They are also aware of advertisements regarding unauthorised Ozempic® and/or semaglutide-containing products spread *via* social media platforms and radio stations. SAHPRA reiterated that Ozempic® is not registered for weight loss in South Africa. A healthcare practitioner may prescribe this product for off-label use as the practitioner would monitor the patient's treatment. Novo Nordisk South Africa, Holder of the Certificate of Registration (HCR), has acknowledged a nationwide shortage of Ozempic® stock, leading to restricted access to treatment for individuals with diabetes. This situation may have opened the door for the influx of falsified or counterfeit products into the market, falsely claiming to be Ozempic® and potentially being used off-label for weight loss. Consumers should exercise caution when encountering online offers for products purporting to be Ozempic® or semaglutide. It is crucial to note that there are currently no generic equivalents of this medicine in South Africa. Therefore, any product not produced by Novo Nordisk and claiming to contain semaglutide is likely to be fraudulent or counterfeit. In South Africa, only one product in two presentations, Ozempic® 0.25 mg and 0.5 mg/dose and Ozempic® 1 mg/dose pens, is registered.[16] On 13 December 2023, SAPHRA released their position on compounded semaglutide products. Semaglutide can be compounded as it is included in a medicine that has been registered by SAHPRA. However, only active ingredients that are included in a product registered by SAHPRA may be used and it must be in accordance with the conditions and requirements contained in the Medicines and Related Substances Act (101 of 1965). It is illegal to compound a medicine using a form of semaglutide that is not in a registered product, e.g. salt forms such as semaglutide acetate and semaglutide sodium, as it has not been reviewed for quality, safety and efficacy.[17] SAHPRA emphasised that these unregistered, substandard and falsified medicines are a serious health risk to the public and encouraged consumers to report any suspected products that are falsely claiming to work like Ozempic®. SAHPRA's 24-hour hotline number is 0800 204 307 or alternatively the web reporting facility: https://bit.ly/3nrku5t can be used.[16,17]

Future outlook

Semaglutide under the tradename Wegovy® is already registered as a weight loss medicine overseas and it may be registered in the future in South Africa as well. This contains higher doses of semaglutide focused on weight loss.[4] Another molecule, tirzepatide, exhibits dual action as a glucose-dependent insulinotropic peptide (GIP) and GLP-1 receptor agonist. Tirzepatide was shown to be dose-dependently more effective compared to GLP-1 RAs, placebo and basal insulin on glycaemic efficacy and body weight reduction. However, it was also associated with an increased incidence of gastrointestinal effects such as nausea. Increased incidences of vomiting and diarrhoea was noted especially with higher dose tirzepatide (15 mg) which caused a higher trial discontinuation rate. All doses were considered safe with regards to serious adverse events and mortality.[18] Tirzepatide, produced by Eli Lilly, is not yet available in South Africa but is registered for weight loss overseas (Mounjaro®, Zepbound®).[19] There is only one orally administered GLP-1 RA currently available; semaglutide tablets 7/14 mg (Rybelsus®), registered only for the treatment of type 2 diabetes, is administered once daily. It is not registered in South Africa, but it is registered for the treatment of type 2 diabetes overseas.[4]

Concluding remarks

The widespread use and promotion of Ozempic® as a popular weight loss medicine and its wide footprint on social media for this purpose has resulted in a shortage of the authentic product. Consequently, unscrupulous individuals have taken advantage of this demand by producing counterfeit medicines which poses a potential danger to consumers. Health regulatory authorities globally are on the lookout for counterfeit products and have warned patients to use only authentic products prescribed by their doctor.

For the time being it is important for health professionals and the public to be aware of the challenges facing this type of diabetes/weight loss medicine. Ozempic® is intended for and registered in South Africa for the treatment of type 2 diabetes. Ozempic® is manufactured

by Novo Nordisk and any other product claiming to be 'Ozempic' or that is called Izempic which is not manufactured by Novo Nordisk is likely to be falsified. It would seem from using the Google search engine that it is currently possible to buy Ozempic®/semaglutide containing products online. It is crucial to avoid taking any medicine that was not prescribed for you, especially when it is acquired from unconventional sources such as social media platforms, online vendors or beauty spas. Doctors make treatment decisions to prescribe medications only after taking a patient's medical history into consideration as those with a genetic predisposition to thyroid cancer for example may be at high risk. The use of every medicine is associated with benefits as well as potential risks, stressing the importance of treatment initialisation under the care of a qualified healthcare professional.

References

1. Boachie MA, Thsehla E, Immurana M, Kohli-Lynch C, Hofman KJ. Estimating the healthcare cost of overweight and obesity in South Africa. Glob Health Action. 2022; 15(1):2045092. https://doi.org/10.1080/16549716.2022.2045092
2. Hu S, Su X, Fan G. Efficacy and tolerability of the subcutaneous semaglutide for type 2 diabetes patients: an updated systematic review and meta-analysis. Diabetol Metab Syndr. 2023; 15:218. https://doi.org/10.1186/s13098-023-01195-7
3. Ozempic (Semaglutide) [Professional Information]. Novo Nordisk, Johannesburg. 2020, 2023. Available at: https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2023/02/approved_pi_ozempic-17Feb2023.pdf Accessed on: 4 January 2024.
4. Murphy A. Ode to Ozempic and friends. Diabetes Focus eMag. 30 May 2023. Available at: https://www.diabetessa.org.za/ode-to-ozempic-and-friends/ Accessed on: 4 January 2024.
5. Trulicity (Dulaglutide) [Prescribing Information]. Eli Lilly and Company, Indianapolis. 2014, 2022. Available at: https://uspl.lilly.com/trulicity/trulicity.html#pi Accessed on: 4 January 2024.
6. Byetta (Exenatide) [Professional Information]. AstraZeneca Pharmaceuticals, Johannesburg. 2008, 2023. Available at: https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2023/09/pi-approved-05.09.2023.pdf Accessed on: 4 January 2024.
7. Bydureon BCise (Exenatide) [Professional Information]. AstraZeneca Pharmaceuticals, Johannesburg. 2008, 2023. Available at: https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2023/06/Final_PI_BydureonBCise_Applicant.pdf Accessed on: 4 January 2024.
8. Victoza (Luraglutide). [Professional Information]. Novo Nordisk, Johannesburg. 2011, 2023. Available at: https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2023/11/Victoza-approved-PI-23-October-2023.pdf Accessed on: 4 January 2024.
9. Saxenda (Luraglutide). [Professional Information]. Novo Nordisk, Johannesburg. 2020, 2022. Available at: https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2022/09/Saxenda-English-Approvd-PI_08Feb22.pdf Accessed on: 4 January 2024.
10. Ozempic FDA approval history. Drugs.com. 2000-2024. Available at: https://www.drugs.com/history/ozempic.html Accessed on: 4 January 2024
11. Fick M. How well-off Brits still buy Ozempic online for weight loss. Reuters. 18 November 2023. Available at: https://www.reuters.com/business/healthcare-pharmaceuticals/how-well-off-brits-still-buy-ozempic-online-weight-loss-2023-11-18/#:~:text=Ozempic%20was%20approved%20for%20type,regulate%20blood%20sugar%20and%20appetite. Accessed on: 4 January 2024.
12. Callahan C. 13 celebrities who've opened up about taking Ozempic or weight-loss drugs. Today Health and Wellness. 15 December 2023. Available at: https://www.today.com/health/celebrities-on-ozempic-rcna129740. Accessed on: 4 January 2024.
13. Ozempic (semaglutide) and Saxenda (liraglutide): vigilance required due to potentially harmful falsified products. Available at: https://www.gov.uk/drug-safety-update/ozempicv-semaglutide-and-saxenda-liraglutide-vigilance-required-due-to-potentially-harmful-falsified-products#:~:text=Ozempic%20(semaglutide)%20has%20been%20authorised,off%2Dlabel%20for%20that%20purpose Accessed on: 4 January 2024.
14. Lovelace Jr. B. Health authorities around the globe issue warnings about fake Ozempic. NBC News. 28 December 2023. Available at: https://www.nbcnews.com/health/health-news/fake-ozempic-health-authorities-globe-issue-warnings-rcna131452 Accessed on: 4 January 2024.
15. Partnership for Safe Medicines. Counterfeit GLP-1 agonists: Injected Diabetes and Weight Loss Medicine. Available at: https://www.safemedicines.org/2023/06/fake-semaglutide.html Accessed on: 4 January 2024.
16. South African Health Products Regulatory Authority (SAHPRA). Public urged to use registered Ozempic products. 11 December 2023. Available at: https://www.sahpra.org.za/news-and-updates/public-urged-to-use-registered-ozempic-products/ Accessed on: 4 January 2024.
17. South African Health Products Regulatory Authority (SAHPRA). SAHPRA's position on semaglutide compounded products. 13 December 2023. Available at: https://www.sahpra.org.za/news-and-updates/sahpras-position-on-semaglutide-compounded-products/ Accessed on: 4 January 2024.
18. Karagiannis T, Avgerinos I, Liakos A, Del Pato S, Matthews DR, Tsapa A, Beklari E. Management of type 2 diabetes with the dual GIP/GLP-1 receptor agonist tirzepatide: a systematic review and meta-analysis. Diabetologia. 2022;65:1251-1261. https://doi.org/10.1007/s00125-022-05715-4
19. Burger L. Lilly's weight-loss drug Mounjaro coming to UK after pen cleared. 25 January 2024. Available at: https://www.reuters.com/business/healthcare-pharmaceuticals/british-regulator-clears-lillys-injection-pen-weight-loss-drug-mounjaro-2024-01-25/ Accessed on: 6 February 2024.