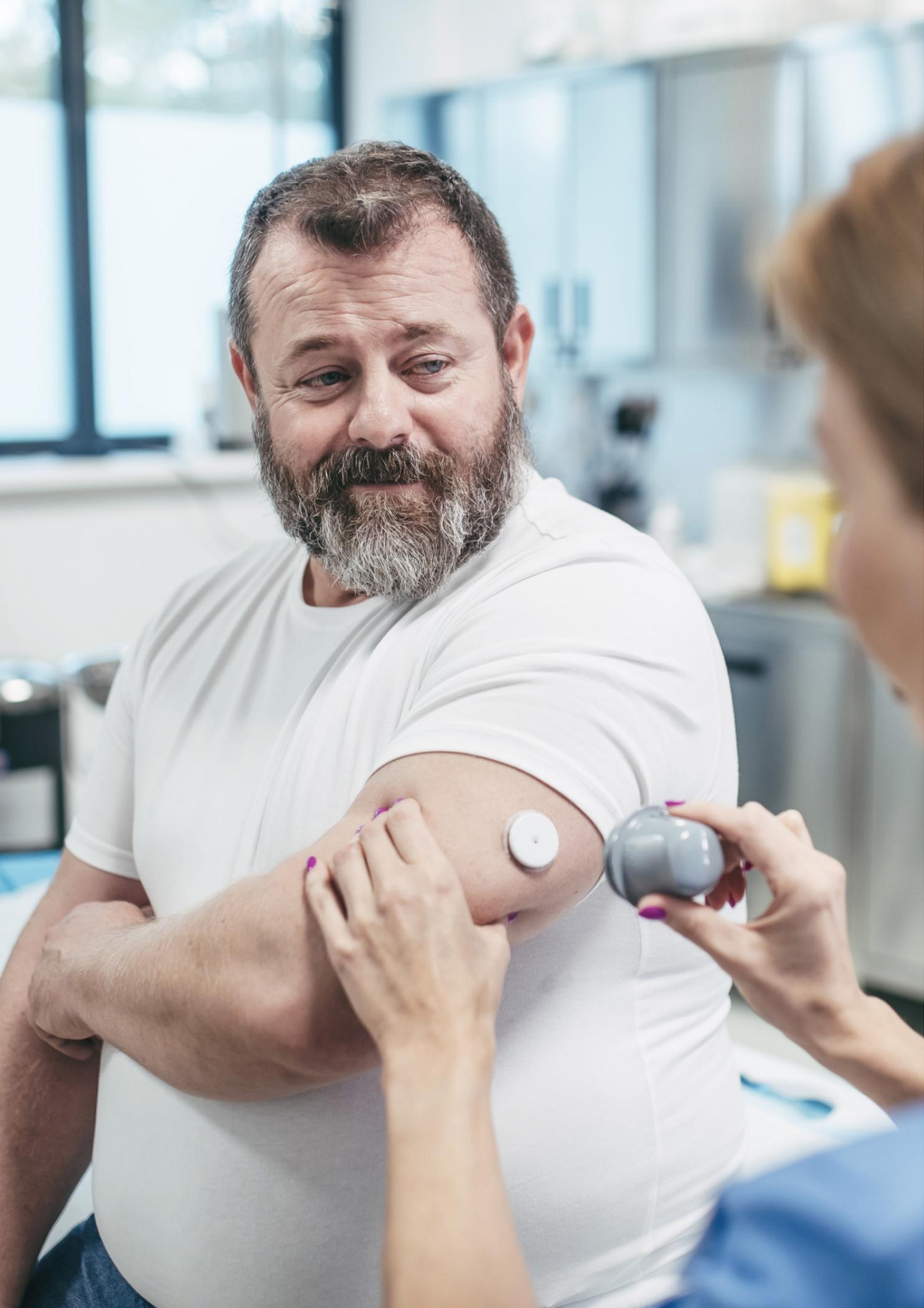




# A NEW FRONTIER IN DIABETES AND WEIGHT MANAGEMENT: **THE RISE OF GLP-1 RECEPTOR AGONISTS**

Report 2024



## INTRODUCTION: THE COST OF DIABETES

With worldwide obesity rates doubling over the past three decades, the growing incidence of Type 2 diabetes presents an escalating public health crisis.

According to recent data from the World Health Organization (WHO), one in eight people in the world live with obesity.<sup>1</sup> Worldwide adult obesity has more than doubled since 1990, while adolescent obesity has quadrupled. Moreover, while overweight was once considered a problem for high-income geographies, it is now growing rapidly in low- and middle- income countries. The amount of overweight African children (aged under 5) has increased almost 23% since the year 2000, for example. Despite this, the prevalence of overweight individuals continues to differ vastly per region, from 31% in South-East Asia and Africa to 67% in the Americas.

Globally, rising levels of overweight are a major concern since obesity is believed to predispose patients to a range of chronic and comorbid medical conditions, including hypertension, heart failure, kidney disease, non-alcoholic steatohepatitis (NASH), cardiovascular disease, and Type 2 diabetes.

In 2014, the WHO reported that 8.5% of all adults had diabetes. In 2019 alone, the disease was the direct cause of 1.5 million deaths globally.<sup>2</sup> Over 95% of diabetics have the variety referred to as Type 2, which affects the body's use of insulin, leading to dangerously high blood sugar levels. While symptoms may go unnoticed for years, the disease can eventually cause nerve damage, foot problems (leading to amputation), loss of vision, kidney disease, heart disease, and stroke.

These complications are taking an enormous economic toll. In the United Kingdom, the National Health System (NHS) spends at least 10% of its entire annual budget on diabetes – 80% of which is spent on treating its complications.<sup>3</sup> In the US, care for diabetes patients accounts for one in four healthcare dollars.<sup>4</sup> According to one study, the total estimated cost of diagnosed diabetes in the US in 2022 was a whopping \$412.9Bn.<sup>5</sup>



<sup>1</sup> <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>

<sup>2</sup> <https://www.who.int/news-room/fact-sheets/detail/diabetes>

<sup>3</sup> <https://www.diabetes.org.uk/about-us/about-the-charity/our-strategy/statistics>

<sup>4,5</sup> <https://pubmed.ncbi.nlm.nih.gov/37909353/>



## GLP-1 RECEPTOR AGONISTS: PAST, PRESENT, FUTURE

A new class of medicine known as GLP-1 agonists is currently revolutionising diabetes and obesity treatment. Their ability to effectively manage blood sugar levels and induce weight loss could be the answer to the public health challenge of obesity.

For more than half a century, an oral medication known as metformin has been the first-line treatment for patients with Type 2 diabetes who are unable to control their blood sugar through lifestyle changes (diet and exercise) alone. The drug reduces the amount of glucose released from the liver and helps the patient's cells to absorb more glucose from the bloodstream. This can be used alone or in combination with insulin injections. It requires daily pills, typically taken with each meal of the day.

More recently, a new type of medication, called GLP-1 receptor agonists, has started changing how we manage Type 2 diabetes. These medications mimic a natural hormone in the body. When blood sugar levels rise, they help the body release insulin and reduce the release of another hormone called glucagon, which lowers blood sugar levels.

GLP-1 receptor agonists also help with weight loss by affecting the brain areas that control hunger and the feeling of being full (satiety), leading

to less food intake. In addition, they slow down digestion, similar to the effect seen with certain weight loss surgeries.

When indicated specifically for weight loss, GLP-1 agonists are generally prescribed in higher doses than for diabetes. Side effects are common, frequently involving gastrointestinal symptoms such as nausea, vomiting, and diarrhoea. GLP-1 agonists may also offer major health benefits beyond weight loss and blood sugar control. New research suggests certain drugs in these groups could help to lower the risk of heart disease, stroke, and kidney disease – although, according to Mayo Clinic, it's not yet clear whether these benefits derive from the medication itself or the associated weight loss. In addition, GLP-1 agonists are undergoing clinical trials for sleep apnoea, Parkinson's disease, Alzheimer's disease, inflammatory bowel disease (IBD) and NASH.

### The evolution of GLP-1 agonists

The history of GLP-1 agonists began in 2005 with the approval of exenatide (Byetta®, Eli Lilly), followed by liraglutide (Victoza®, Novo Nordisk) and dulaglutide (Trulicity®, Eli Lilly) in 2010 and 2014 respectively. Formulation advancements over the last two decades enabled pharmaceutical companies to transition from twice-daily injections (exenatide) to daily (liraglutide) and eventually the once-weekly preparations that are now dominating the market. This in turn reduced the burden of frequent injections for the patient, representing a significant advantage over earlier formulations.

Trulicity was the first GLP-1 injection with a once-weekly dosing schedule to achieve commercial success. It comes in a carton of four different single-dose injection pens. In 2017, the US Food and Drug Administration approved a similar drug called semaglutide (Ozempic®, Novo Nordisk), indicated for the treatment of Type 2 diabetes. Ozempic was made available as a multi-use pen, containing four doses for each week of the month.

While liraglutide was the first GLP-1 agonist approved for obesity (under the brand Saxenda®), it was not nearly as effective as the newer versions. In mid-2021, the FDA approved Novo Nordisk's semaglutide injection as a chronic weight management treatment under the brand name Wegovy®. In one trial of overweight adults without diabetes, participants who received Wegovy lost an average of 12.4% of their initial bodyweight.<sup>6</sup>

The FDA approved Eli Lilly's tirzepatide injection, Mounjaro®, in 2022. According to the originator, Mounjaro is the first and only FDA-approved "single molecule that activates the body's receptors for GIP and GLP-1, which are natural incretin hormones."<sup>7</sup> This made it the first dual agonist, potentially making tirzepatide more efficacious than its competitors. Tirzepatide was FDA approved for chronic weight management under the brand name Zepbound® a year later. This

decision was backed by clinical trial data in adults without diabetes, which experienced an average reduction of 18% of body weight when taking 15mg weekly doses of Zepbound. In addition, in a separate study of adults with Type 2 diabetes, the average weight loss for those on 15mg weekly Zepbound injections was 12%.<sup>8</sup>

We are now in a new era of obesity treatments where combinations of APIs (ie. dual agonists) can approach the weight loss achieved with bariatric surgeries such as gastric bypass. Although such surgeries can result in an average of 25–30% weight loss as well as long-term weight maintenance, they are very difficult to scale at the population level. In addition, not all patients are open to the possibility of surgical intervention due to the risk of postoperative complications.

Other combinations of GLP-1 agonists, including Novo Nordisk's CagriSema and the triple agonist retatrutide (Eli Lilly), have also progressed to Phase 3 trials as obesity treatments. Initial data suggests they may lead to even greater weight loss than tirzepatide.

While Novo Nordisk and Eli Lilly currently dominate the market, other players have seen success in the development of GLP-1 agonists. Zealand Pharma and Boehringer Ingelheim are working together on a drug called survodutide that targets GLP-1 and glucagon. This candidate has also produced very encouraging early results, with Phase 3 study data expected in late 2025.

Meanwhile, patents have expired for Victoza, opening the doors for other companies to begin creating generic versions of liraglutide. In March 2024, Biocon Limited received approval for its liraglutide biosimilar, while Teva Pharmaceuticals recently announced the launch of the first generic GLP-1 agonist in the US. Three other manufacturers are currently working on liraglutide generics, including Pfizer, Mylan, and Sandoz, and these are expected to launch soon in the US.



<sup>6</sup> <https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014>

<sup>7</sup> <https://investor.lilly.com/news-releases/news-release-details/fda-approves-lillys-mounjaro-tirzepatide-injection-first-and>

<sup>8</sup> <https://www.fda.gov/news-events/press-announcements/fda-approves-new-medication-chronic-weight-management>

# THE GLP-1 AGONIST MARKET: SALES FORECASTS AND KEY EVENTS

Demand is soaring for GLP-1 agonists, with manufacturers struggling to keep up. By 2033, GlobalData predicts this class of drugs to bring in global sales of \$168bn.

According to a recent GlobalData report titled Glucagon-Like Peptide-1 Receptor (GLP-1R) Agonists in Type 2 Diabetes and Obesity: 68-Market Analysis and Sales Forecast, total sales for GLP-1 agonists across the 68 markets covered in the report hit \$39.2bn in 2023. By 2033, this is expected to rise to \$168bn. North America is forecast to account for the overwhelming majority of these sales, as shown in the pie charts in Figure 1. The second largest market will be Europe, representing 15% of the sales.

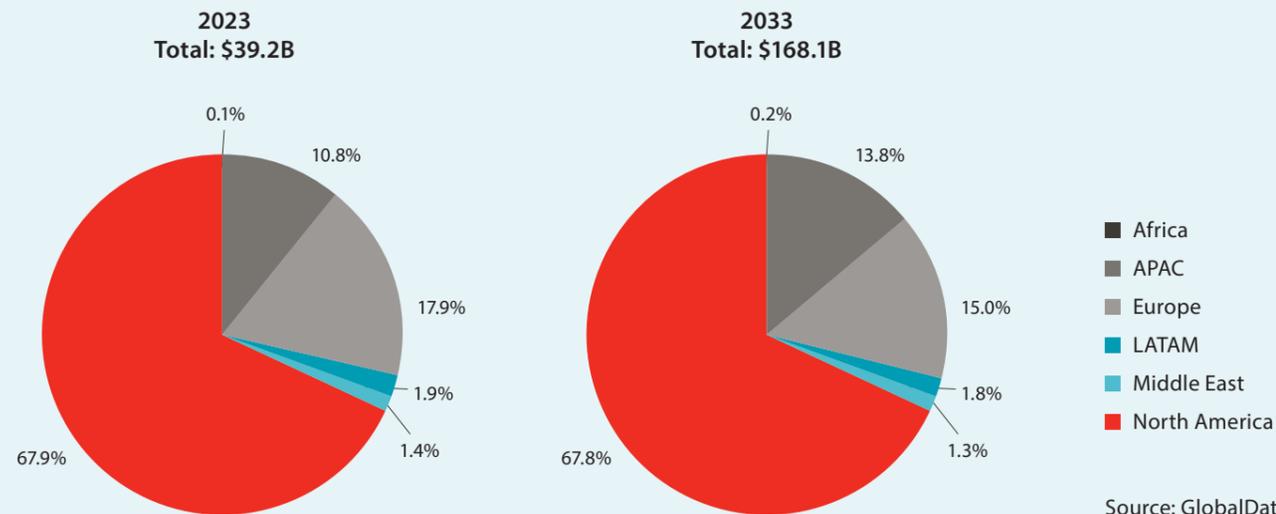
GlobalData expects this upward trajectory to be driven by a range of key events occurring in the seven major pharmaceutical markets, including the expected launch of CagriSema and IcoSema in the US, Japan and the EU across 2025 and 2026. In 2027, further launches of Novo Nordisk's oral semaglutide (NN-9932), both Eli Lilly's retratutide injection and orforglipron calcium (an oral nonpeptide GLP-1 agonist),

and Boehringer Ingelheim's survodutide injection will also contribute to market growth. Meanwhile, upcoming patent expiries will slightly slow growth, with patents for Novo Nordisk's Saxenda/Victoza already starting to expire in 2023.

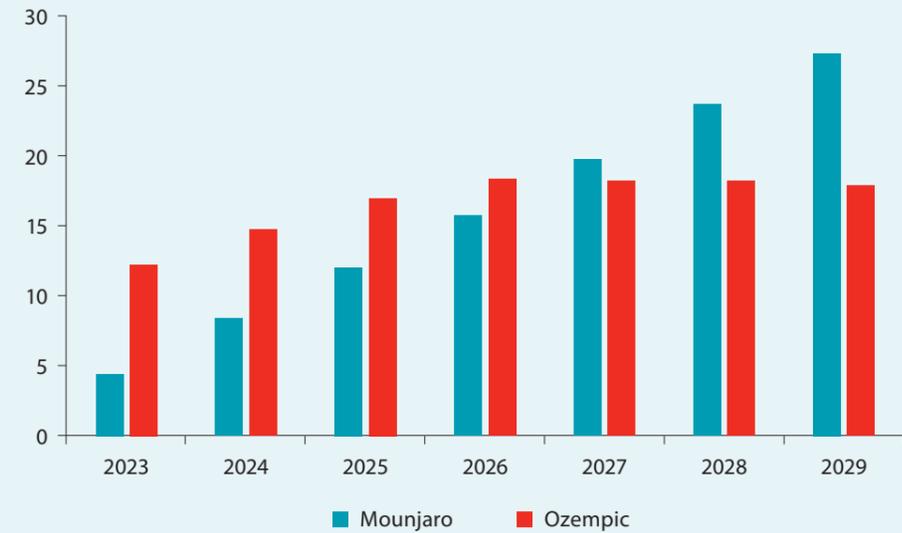
In the short term, Ozempic is expected to dominate sales, having secured its approval five years ahead of Mounjaro. However, in December 2023, GlobalData forecast Mounjaro sales to overtake those of Ozempic by 2027, making it the leading drug by sales in the obesity and diabetes space.

While the market is currently led by Novo Nordisk and Eli Lilly, GlobalData analysts believe there are opportunities for other players to enter "as the patient population that can benefit from this type of molecule is so large," notes Costanza Alciata, Msc, Analyst, CVMD,

**FIGURE 1: GLP-1R AGONISTS' TYPE 2 DIABETES AND OBESITY MARKET SIZE ACROSS THE 68M, BY GEOGRAPHICAL REGION**



**FIGURE 2: MOUNJARO AND OZEMPIC, CONSENSUS SALES FORECAST (2023 TO 2029)**



Source: GlobalData, as of December 5th, 2023

GlobalData. Moreover, with GLP-1 agonists showing "great potential" in other disease areas, not only metabolic but also neurological, she believes "the GLP-1 market could grow even further."

Despite the successes, the market faces major challenges relating to access and supply. In the US, the high cost of this new class of medicine has sparked debate, with a month's supply of Ozempic and Mounjaro both priced around the \$1,000 mark. The weight management brands are pricier still, with Wegovy listed at \$1,349 per month.<sup>9</sup> Currently, private insurers tend not to cover off-label prescriptions and often prefer to avoid covering GLP-1 agonists completely, while Medicare (the federal health insurance program in the US) is not permitted to cover any weight management treatment. This means patients must pay out of pocket, making the therapies inaccessible for many.

Meanwhile, skyrocketing demand for GLP-1 agonists has outstripped supply. Product shortages have plagued Wegovy ever since its US launch in 2021. There have also been global shortages of certain doses of Ozempic as demand for the low-dose versions (0.25/0.5mg) accelerated at a greater pace than anticipated. This was due to off-label prescriptions of the diabetes drug, leaving some of the most vulnerable patients with disruptions in care.

Novo Nordisk has advised there would be intermittent supply of all strengths of Ozempic throughout 2024. To limit disruptions in care for diabetes patients, the Therapeutic Goods Administration has advised prescribers to initiate new patients on Ozempic only when necessary and to consider whether those already on Ozempic could be changed to an alternative medication. This would help to conserve supplies for the patients with no alternative options. Eli Lilly faces similar manufacturing challenges, with both Zepbound and Mounjaro in short supply through 2024.

<sup>9</sup> <https://www.theguardian.com/business/2024/jan/31/obesity-drug-ozempic-novo-nordisk-record-wegovy>



## PRIMARY PACKAGING: THE NEED FOR PEN INJECTORS AND AUTO-INJECTORS

The rapid growth of the GLP-1 market is raising the demand for high-quality primary packaging solutions that make self-administration safe and simple for patients.

As with any injectable drug, primary packaging is a huge factor in the safety and efficacy of the product that patients receive. Since GLP-1 agonist treatment regimens typically require regular and ongoing injections administered by the patient themselves, there was another major factor at play here: convenience. With 40 years of history and a strong presence in the diabetes market, pen injectors represent the ideal solution. Since the introduction of GLP-1 agonists for obesity care, auto-injectors have also emerged as an important option.

While vials are still used for the primary packaging of GLP-1 agonists, they are not particularly convenient, requiring several steps to prepare and administer the drug. There is a higher risk for contamination due to multiple needle entries. Moreover, vials are less convenient to carry and use on-the-go compared to prefilled options (prefilled syringes or cartridges).

Cartridges are used in combination with pen injectors, while prefilled syringes can be used as a stand-alone. To further improve convenience for the patient, prefilled syringes are used in combination with an auto-injector on an increasing basis.

For diabetic care, it is important that the injected dose can be set based on a comprehensive evaluation of the patient's blood glucose patterns, lifestyle and specific needs, guided by healthcare professionals. This is only possible with a pen injector. For obesity care, the dose is more fixed. In this case, both a pen injector and an auto-injector can be used. The pen injector offers the possibility to serve multiple injections (of the same dose) while an auto-injector can only be used once.

Plungers are a fundamental component of the device's mechanism, impacting not only the functionality of the device but also the container closure integrity (CCI), since they act as a seal for the drug product. Datwyler's plunger designs ensure a consistent break loose and gliding force and limited plunger movement during air transport, which is important to ensure sterility of the drug product. Besides plungers, combiseals (which seal the cartridge at the other side) are another important component to protect the contents of the cartridge from contamination and leaks, even after multi-piercing with a needle.

Datwyler plungers and combiseals are made of a specialised halobutyl-based formula which ensures an optimised extractable and leachable (E&L) profile, guaranteeing the stability of the drug product over the shelf life and safeguarding patient health. To achieve the highest-quality sealing solution for cartridges, the combiseals can be finished with a protective laminate technology. The company's DuraCoat™ solution improves the seal's durability during handling processes, reducing the incidence of flaking seen with standard epoxy-based lacquer, which can eventually contaminate the drug product. The protective laminate also significantly reduces the particle generation that can occur with standard lacquered aluminium during deep drawing, assembly, washing and crimping.

### Conclusion

The global obesity and diabetes epidemic presents a major public health challenge, with obesity rates soaring and diabetes now a widespread issue across all regions of the world. The rise of GLP-1 receptor agonists marks a significant advancement in diabetes management and obesity treatment, providing effective blood sugar control as well as notable weight loss benefits. The primary packaging of these drugs plays a crucial role in ensuring their safety, efficacy, and convenience.

Manufacturers are up against countless challenges as demand continues to rise for this new class of medicine, but the availability of high-quality, reliable primary packaging components need not be one. With an extensive portfolio of cartridge and prefilled syringe solutions and a global manufacturing footprint, Datwyler's industry leading parenteral packaging solutions can be trusted to deliver.





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