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PERSPECTIVE ON THE Rx PIPELINE

Understanding changes in the medication market and their impact on cost and care.

elixir
CRAFTED Rx SOLUTIONS

Perspective on the Rx Pipeline

Elixir continuously monitors the drug pipeline. As treatment options change, we evaluate and share our perspective on the clinical benefits, cost-effectiveness and overall impact to payers and patients. Our Perspective on the Rx Pipeline report provides ongoing actionable insights from our team of clinical experts and the steps we are taking to protect and improve plan performance.

INCLUDED IN THIS EDITION:

Developments in Diabetes Medications: The Many Benefits of GLP-1 Agonists

DIABETES AND GLP-1 AGONISTS

Developments in Diabetes Medications: The Many Benefits of GLP-1 Agonists

TIMING

When will payers be impacted?

NOW | 1 YEAR | 5 YEARS+

CLINICAL EFFECTIVENESS

Compared to available options, is this drug better for treatment?

UNPROVEN | EQUIVALENT | BETTER

MEMBER EXPERIENCE

Will this positively or negatively impact members?

MINOR DISRUPTION | NO CHANGE | MAJOR DISRUPTION

NEGATIVE SATISFACTION | NO CHANGE | POSITIVE SATISFACTION

PAYER IMPACT

How will this influence Rx spend?

DECREASE PER Rx | NO CHANGE | INCREASE PER Rx

DECREASE TOTAL SPEND | NO CHANGE | INCREASE TOTAL SPEND

Situation Summary

Diabetes is a growing concern in the United States, with 35 million individuals impacted by type 2 diabetes mellitus (T2DM).[1] This chronic condition can lead to other health complications. In fact, people with diabetes are twice as likely to have heart disease or stroke.[2] The leading cause of morbidity and mortality for individuals with diabetes is atherosclerortic cardiovascular disease (CVD), which includes coronary heart disease, cerebrovascular disease or peripheral arterial disease.

Initial therapy for individuals with T2DM who are at high risk for CVD, heart failure (HF) and/or chronic kidney disease is metformin and a glucagon-like peptide 1 (GLP-1) or sodium glucose transporter ligand 2 (SGLT-2). GLP-1 and SGLT-2 have the highest level of clinical evidence for use in this population, per the American Diabetes Association (ADA) guidelines.[3]

Both GLP-1 and SGTL-2 products, such as Jardiance®, have the ability to improve blood glucose control (hemoglobin A1c reduction), potentiate weight loss and provide a cardiovascular protective effect. Previously approved diabetes drugs were weight neutral or caused weight gain, a concern because obesity is often a co-morbidity of T2DM and can increase the risk for a cardiovascular complication, such as a heart attack or stroke.

The first GLP-1 was FDA approved in 2005 as a twice-daily injection indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM (these products are not approved for those with type 1 diabetes). Approval of additional GLP-1 agonists has reduced injection burden to weekly and recently an oral GLP-1 product was approved. This is an impactful advancement in T2DM management, as some diabetics may be managing multiple injections per day if on insulin. Weekly or oral therapy has helped to reduce their daily injection burden, allowing for improved adherence and a better experience in managing T2DM.

With the finding of weight loss, manufacturers studied higher doses and entered applications for use of the chemical entities for weight loss products. Both Wegovy® and Saxenda® are anti-obesity medications that can be used without the diagnosis of T2DM.

It is important to note that GLP-1 products are not without side effects, often as nausea, diarrhea and vomiting, which may limit utility in some individuals.

Following is a summary of the growing GLP-1 market[4-16]:

DIABETES AND GLP-1 AGONISTS

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GLP-1 Medication Options

GLP-1 Name	Mfg	Dose Frequency, Route of Administration	FDA Labeled CVD Benefit	Average A1C Reduction	Average Short-Term Weight Loss	Weight Loss with Same Chemical Entity	Considerations
Adlyxin® (lixisenatide)	Sanofi-Aventis	Daily, subcutaneous (SC)	No	~1%	~2 kg	N/A	Soliqua® (insulin glargine/lixisenitide): Combination product of set dose long-acting insulin and GLP-1 available; however, market uptake not as aggressive as predicted (2.5 kg weight loss versus insulin degludec alone).
Byetta® (exenatide)	AstraZeneca	Twice daily, SC	No	~1%	~2 kg	N/A	Significant GI adverse effect, recommended to be injected 60 minutes prior to meal.
Bydureon BCise (exenatide) extended release	AstraZeneca	Weekly, SC	No	~1.4%	~1.4 kg	N/A	Pediatric indication for 10 years and older.
Ozempic® (semaglutide)	Novo Nordisk	Weekly, SC	Reduces major CV events in those with **established** CVD	~1.5%	~4 kg	Wegovy, weekly	Same chemical entity as Rybelsus. A supplemental new drug application (sNDA) was approved for Ozempic 2 mg on March 28. In the clinical trial SUSTAIN FORTE, Ozempic 2 mg weekly was found to have an A1c reduction of approximately 2%.
Rybelsus® (semaglutide)	Novo Nordisk	Daily, oral	No	~1%	~2.5 kg	N/A	First oral GLP-1.
Trulicity® (dulaglutide)	Eli Lily	Weekly, SC	Risk reduction in all T2DM, **regardless** of prior CVD	~1.5% to 1.8% at maximum dose of 4.5 mg weekly	~2.5 to 4.6 kg at maximum dose of 4.5 mg weekly	N/A	Additional doses approved in 2020 that had more significant weight loss and A1c improvement.
Victoza® (liraglutide)	Novo Nordisk	Daily, SC	Reduces major CV events in those with **established** CVD	~1.5%	~2 kg	Saxenda, daily	Xultophy® combination product; generic Victoza anticipated in 2024.

DIABETES AND GLP-1 AGONISTS

PIPELINE STAGE

GLP-1 Pipeline

The diabetic pipeline, and specifically those with a GLP-1 agonist mechanism of action, are catching attention in the prescription pipeline.

Notable GLP-1 Product Pipeline[17-19]

GLP-1	Mfg	Route of Administration	Mechanism of Action	Status	Clinical Insight
LY3298176 Tirzepatide	Eli Lilly	SC	GIP/GLP-1	PDUFA* Pending (2Q 2022)	First indication for T2DM Other upcoming indications may include treatment of: chronic heart failure with preserved ejection fraction, obesity and reduction of adverse CVD outcomes Once weekly injection SURMOUNT-1, a clinical trial for obesity, may have data by April 2022 regarding a percent change from baseline in body weight
Rybelsus® (semaglutide) 25, 50 mg	Novo Nordisk	Oral	GLP-1	Phase III	Clinical studies are examining if higher doses can be tolerated in type 2 diabetics with better efficacy
PF-06882961 Danuglipron	Pfizer	Oral	GLP-1	Phase II	Another oral GLP-1
MEDI 0382 Cotadutide	AstraZeneca	SC	GLP-1/ glucagon dual agonist	Phase II	Improved glycemic control in T2DM Obesity, non-alcoholic steatohepatitis (NASH), and diabetic kidney disease indications also in the pipeline

* PDUFA stands for Prescription Drug User Fee Act, which was enacted by Congress in 1992 to authorize the FDA to collect fees from pharmaceutical manufacturers to aid in expediting the drug approval process.

DIABETES AND GLP-1 AGONISTS

Tirzepatide is the closest pipeline product to a possible FDA approval in the upcoming weeks. The SURPASS-4 clinical trial was a non-inferiority study comparing tirzepatide to insulin glargine where tirzepartide showed superior A1c and body weight reductions from baseline in adults with T2DM at increased CVD risk.[20] Also, tirzepatide reported a higher occurrence of individuals achieving an A1c below 7% compared to insulin glargine.

Another open-label, randomized phase III inferiority study looked at mean A1c reduction in type 2 diabetics not controlled on metformin when treated with semaglutide or tirzepatide and tirzepatide was again found non-inferior (and even superior) in reducing A1c. Weight loss results were favorable as well for tirzepatide. It should be noted that only semaglutide injection (not oral) was compared to tirzepatide, and higher doses of semaglutide were not compared to tirzeparatide.[21]

The mean A1c reduction from baseline was above 2% and weight reduction was near 10 kg (22 lbs) in tirzepatide clinical studies, exceeding current FDA-approved GLP-1 products. Like other GLP-1 products, the most common adverse event was gastrointestinal side effects (nausea, vomiting, diarrhea), which tended to decrease over time.

The Institute for Clinical and Economic Review's (ICER's) *Tirzepatide for Type 2 Diabetes Final Report* stated tirzepatide shows impressive impact on glucose lowering and glycemic control. Durability of tirzepatide for long-term weight loss and glycemic control are still under study and not yet proven. ICER did have concerns that there was a lack of minorities represented in clinical trials. When reviewing tirzepatide to other products for diabetes, its efficacy is promising as seen in the following table.

ICER Evidence Ratings - Health Benefits of Tirzepatide vs Comparator[22]

	Comparator	**Evidence Rating** (tirzepatide over comparator)
Tirzepatide	Background Therapy (metformin +/- sulfonylureas or thiazolidinediones)	B+
	Injectable Semaglutide	C+
	Empagliflozin	C++

B+ = incremental or better, C+ = comparable or incremental, C++ = comparable or better

The New England Comparative Effectiveness Public Advisory Council (CEPAC), a nationally recognized independent appraisal committee for ICER, found that adding tirzepatide to background therapy is superior to background therapy alone in a vote of 13 yes to 0 no. Votes were split when asked if it was superior to Ozempic (semaglutide), and votes favored "no" when asked if tirzepatide was superior to Jardiance (empagliflozin).

GLP-1 Generic Opportunity

Currently GLP-1 agonists are all branded products. Byetta (a twice daily dosed GLP-1), which is patent and regulatory exclusivity free, has multiple manufactures filing for generic approval, but there has been no movement on FDA approval yet. Victoza may have a loss of exclusivity near 2024; however, Victoza is once daily subcutaneous dosing and many people may be accustomed to once weekly or oral daily dosing. It may be difficult to move people back to less convenient administration.[23, 24]

DIABETES AND GLP-1 AGONISTS

PIPELINE STAGE

PAYER ACTION PLAN

- **Monitor the Drug Pipeline**
  At this time, there is no action that payers need to take. Elixir will continue to monitor the GLP-1 drug pipeline and keep our clients apprised of updates. Our P&T committee will review any newly approved FDA products and update clients when these products may be available for member utilization.

Impact to the Pharmacy Care Experience

The GLP-1 class has had significant growth in the last five years and already has multiple effective products with robust clinical data in the diabetes space, including once weekly subcutaneous administration and oral products. Thus, those on stable products may not be quick to switch, and tirzepatide is still a weekly injection versus oral treatment option. However, tirzepatide may result in better A1c lowering and more weight loss compared to other current GLP-1s and an additional indication for weight loss in the future could increase uptake. Clients may see new-start members elect to use tirzepatide as well.

Cost may be comparable to current GLP-1 or slightly more due to proposed increases in efficacy and weight loss parameters. Regardless, it will be a significant revenue generator for the pharmaceutical manufacturer if approved in 2022.

Pipeline Monitoring: Elixir will continue to closely monitor the drug pipeline of diabetes medications and GLP-1 products.

Pharmacy & Therapeutics Review and Formulary Strategies: GLP-1 is often a highly managed drug class, as far as preferred products. With many products showing CVD benefit, considerable T2DM parameter improvement and weight loss, preferring one product to another can be expected. Keeping a close eye on any weight loss indications is also imperative, as many clients chose to include or exclude weight loss treatment as a benefit election.

Elixir's Pharmacy & Therapeutics (P&T) committee, which helps determine formulary placement, will rigorously review each future FDA approval to assure clinically appropriate, safe and efficacious products are provided on the formulary and add value.

DIABETES AND GLP-1 AGONISTS

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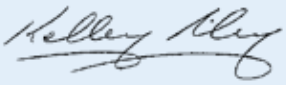
Our Clinical Steering Committee

The Elixir Clinical Steering Committee brings together leaders from across our national pharmacy care company to monitor the drug landscape, provide recommendations on how to address changes, and to ensure our clients and patients are prepared—in advance.

With any new development, we partner with our Pharmacy & Therapeutics (P&T) committee and consult with our best-in-class specialty pharmacy, to provide a balanced perspective on the clinical effectiveness of all available options, the cost impact to our plan sponsors and patients, and the impact on the overall patient experience.



Kel Riley, MD
Chief Medical Officer

More ways to improve member and plan outcomes

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