



HHSC Psychiatric Executive Formulary Committee Minutes

The HHSC Psychiatric Executive Formulary Committee (PEFC) convened on July 8, 2022 via MS Teams. The meeting was called to order by Dr. Moron, Chair at 9:30 a.m.

Members

Member Names	Attendance	Member Names	Attendance
Yekini Adeyemi, RN	Present	David Moron, MD- Chair	Present
Angela Babin, RPh	Present	Leah Nunez, PharmD	Present
Jean Baemayr, PharmD- Secretary	Present	Brittany Parmentier, PharmD	Present
John Bennett, MD	Present	Kenda Pittman, PharmD	Present
Giovanna Betancourt, PharmD	Present	Rishi Sawhney, MD	Absent
Rakesh Chadalavada, MD	Present	Charlene Shero, MD	Absent
German Corso, MD	Present	Glenn Shipley, DO	Present
Brad Fitzwater, MD	Absent	Lesia Trickett, MD	Absent
Catherine Hall, PharmD	Present	Ashton Wickramasinghe, MD	Present
Dana Hopkins, RN	Present	Patrick Young, MD	Present
Jeffery Matthews, MD	Present		

Guests Present: Tonya Barrios, PhTR, State Hospitals Central Administration; Heather Cooper, PharmD, The Harris Center for Mental Health and IDD; Holly Cumbie, PharmD, The Harris Center for Mental Health and IDD

Opening

Introduction and Other Information

Dr. Baemayr will be retiring as of July 31. Kasey Pena, PharmD, will be the incoming State Hospital Chief Pharmacist and Secretary of this committee.

Conflict of Interest Disclosures

The committee members present did not disclose any new conflicts of interest.

Review of Minutes

The minutes from the April 22 meeting were approved as previously distributed.

Unfinished Business

None

New Business

Adverse Drug Reaction Reports

None received.

New Drug Applications

Dulaglutide (Trulicity)

Presented by Dr. Hall. Please refer to Appendix A for the monograph that was considered when determining action by the committee.

After discussion of the monograph, the committee approved the addition of dulaglutide to the formulary in the Miscellaneous Antidiabetic Agents section.

The formulary check list was completed and no issues were detected.

After a presentation on the comparison of GLP-1 Ra agents, the committee agreed to consider the addition of Ozempic (semaglutide) to the formulary. Dr. Hall will prepare a monograph for presentation at the next meeting.

Ginkgo Biloba- pended

Invega Trinza- pended

Quarterly Non-Formulary Drug Justification Report

For the third quarter of fiscal year 2022 (March 2022 to May 2022), only the state hospitals reported use of non-formulary agents. The state supported living centers (SSLCs) currently do not have the capability to obtain non-formulary drug usage reports from their computer system but are working with the vendor to make this reporting possible. The following were the top five non-formulary agents, by number of orders, that were prescribed in the state hospitals during the third quarter of fiscal year 2022:

- Quercetin
- Magnesium oxide
- Acetaminophen/caffeine/pyrilamine (Midol Menstrual Complete)
- Listerine Zero
- Molnupiravir

After a review of non-formulary use data, the committee agreed to consider the addition of clonidine ER to the formulary. A monograph will be prepared for presentation at the next meeting.

Drug Formulary Sectional Review

In reviewing the formulary drug listings for Dermatologicals (Acne agents through Burns Agents), the following changes were approved:

- Anti-Infectives-Antibiotics and Burn Agents sections
 - Remove: Bacitracin injection
- Anti-Infectives-Antifungals
 - Remove: Miconazole- injection powder
- Antiseptics & Germicides
 - Remove: Hexachlorophene
- Updated Cost Index of several items

The updated formulary will be posted on the PEFC website.

Other Formulary Changes

The committee also approved the following change to the formulary:

- Remove gentamicin injection, intrathecal, preservative-free from the Infectious Disease Agents- Antibiotics-Aminoglycosides section.

The updated formulary will be posted on the PEFC website.

Psychotropic Medication Audit Criteria & Guidelines Review

The committee reviewed and approved recommended revisions to the following audit criteria document:

- Tricyclic Antidepressants

The updated documents will be posted to the PEFC website.

Psychotropic Monitoring Guidelines Review

The committee reviewed and approved updates to the Psychotropic Monitoring Guidelines that were based on revisions to the audit criteria approved at this meeting.

Benzodiazepine Safety and Tapering Guidelines

Dr. Heather Cooper presented a reference document she created regarding benzodiazepine tapering. The committee felt the document would be a useful addition to the **Resources** section of the PEFC website.

Issues from the Chief Medical Officer, State Hospitals

Dr. Matthews had no issues to report.

Issues from the Medical Services Coordinator, SSLCs

Dr. Shipley reported that there has been a slight increase in COVID cases at the SSLCs, but the current variant appears to be causing less severe disease.

Drug Shortages, Recalls, and FDA Safety Communications

The FDA has issued the following safety communications and recalls that may impact our facilities:

Shortages

Lorazepam injection:

Current shortage due to manufacturing delays and increased demand.

Safety-related Labeling Changes

Nirmatrelvir/ritonavir (Paxlovid):

The FDA "...is aware of the reports of some patients developing recurrent COVID-19 symptoms after completing a treatment course of Paxlovid. In some of these cases, patients tested negative on a direct SARS-CoV-2 viral test and then tested positive again. The benefit of a 5-day treatment course of Paxlovid was demonstrated in the clinical trial that supported the EUA. This study showed that among non-hospitalized patients at high risk of progression to severe disease, treatment with Paxlovid reduced the risk of hospitalization or death by 88%. In light of these reports, additional analyses of the Paxlovid clinical trial data have been performed. In the Paxlovid clinical trial, some patients (range 1-2%) had one or more positive SARS-CoV-2 PCR tests after testing negative, or an increase in the amount of SARS-CoV-2 detected by PCR, after completing their treatment course. This finding was observed in patients treated with the drug as well as patients who received placebo, so it is unclear at this point that this is related to drug treatment. Additional analyses show that most of the patients did not have symptoms at the time of a positive PCR test after testing negative, and, most importantly, there was no increased occurrence of hospitalization or death or development of drug resistance. These reports, then, do not change the conclusions from the Paxlovid clinical trial which demonstrated a marked reduction in hospitalization and death. We are continuing to review data from clinical trials and will provide additional information as it becomes available.

However, there is no evidence of benefit at this time for a longer course of treatment (e.g., 10 days rather than the 5 days recommended in the Provider Fact Sheet for Paxlovid) or repeating a treatment course of Paxlovid in patients with recurrent COVID-19 symptoms following completion of a treatment course.

Buprenorphine, buprenorphine/naloxone (Subutex, Suboxone):

Warnings and Precautions: *Newly added subsections:* Dental Adverse Events: Cases of dental caries, some severe (i.e., tooth fracture, tooth loss), have been reported following the use of transmucosal buprenorphine-containing products. Reported events include cavities, tooth decay, dental abscesses/infection, rampant caries, tooth erosion, fillings falling out, and, in some cases, total tooth loss. Treatment for these events included tooth extraction, root canal, dental surgery, as well as other restorative procedures (i.e., fillings, crowns, implants, dentures). Multiple cases were reported in individuals without any prior history of dental problems.

Refer patients to dental care services and encourage them to have regular dental checkups while taking SUBUTEX. Educate patients to seek dental care and strategies to maintain or improve oral health while being treated with transmucosal buprenorphine-containing products. Strategies include, but are not limited to, gently rinsing the teeth and gums with water and then swallowing after SUBUTEX has been completely dissolved in the oral mucosa. Advise patients to wait for at least one hour after taking SUBUTEX before brushing teeth.

Patient Counseling Information: *Additions and/or revisions underlined:*

- Advise patients that, after SUBOXONE has completely dissolved in the oral mucosa, to take a sip of water, swish it gently around their teeth and gums, and swallow. Advise patients to wait for at least one hour after taking SUBOXONE before brushing teeth.
- Refer patients to dental care services and encourage them to have regular dental checkups while taking SUBOXONE. Instruct patients to inform their dentist that they have started therapy on SUBOXONE.

Warnings and Precautions: Additions and/or revisions underlined: QTc Prolongation: Thorough QT studies with buprenorphine products have demonstrated QT prolongation < or equal to 15 msec. This QTc prolongation effect does not appear to be mediated by hERG channels. Based on these two findings, buprenorphine is unlikely to be pro-arrhythmic when used alone in patients without risk factors. The risk of combining buprenorphine with other QT-prolonging agents is not known.

Consider these observations in clinical decisions when prescribing SUBLOCADE to patients with risk factors such as hypokalemia, bradycardia, recent conversion from atrial fibrillation, congestive heart failure, digitalis therapy, baseline QT prolongation, subclinical long-QT syndrome, or severe hypomagnesemia.

News Briefs

The following information was shared with the committee members:

FDA Approves Dexmedetomidine for Agitation From Bipolar Disorders, Schizophrenia

[Pharmacy Times](#) (4/7, Gallagher) reports, "The FDA has approved dexmedetomidine (Igalmi, BioXcel Therapeutics) sublingual film for the treatment of adults with agitation associated with bipolar disorders 1 and 2 and schizophrenia." BioXcel plans to launch the drug in the United States in the second quarter of 2022.

Dexmedetomidine is an alpha-2 agonist with sedative and analgesic properties and "...although there were no serious AEs in the studies, it can cause bradycardia, dizziness, dry mouth, hypotension, oral hypoesthesia, orthostatic hypotension, paresthesia, QT interval prolongation, and somnolence."

Nasal Spray to Treat Anxiety Moves Forward in Phase 3 Trial

[Healio](#) (4/15, Downey) reports, “VistaGen Therapeutics and AffaMed Therapeutics announced a global phase 3 trial to assess the efficacy, safety and tolerability of a nasal spray that treats adults with social anxiety disorders. Dubbed the PALISADE Global trial, the companies have submitted necessary data to the FDA under its existing PH94B investigational new drug application for the nasal spray. The trial is expected to begin in the United States and China in the second half of 2022. Additional reporting [Healio](#) (Herpin 5/13): “According to a press release from VistaGen, the FDA stated that both nonclinical and clinical data from the PALISADE phase 3 program found that receptor binding data do not show that PH94B has affinity for abuse-related sites, such as dopamine, opiate, and no additional nonclinical studies are required to evaluate the drug’s abuse potential.” From [VistaGen Therapeutics, Inc](#): “PH94B nasal spray is fundamentally different from all current drug treatments for SAD. PH94B activates nasal chemosensory neurons that trigger neural circuits in the brain that suppress fear and anxiety.”

Aim To Make Alzheimer’s Disease Treatments More Affordable To Expand Access

[The Hill](#) (4/27, Schoenbaum) reports that on Tuesday, lawmakers “said too many hurdles remain between” patients with Alzheimer’s disease “and emerging medications that could slow their deterioration, due to both the high cost of new drugs and the limited response from Congress and regulatory agencies to expand access to them.” Lawmakers in June “introduced the bipartisan Comprehensive Care for Alzheimer’s Act” that “would create a new payment model for dementia treatment under Medicare to make care more affordable.”

FDA Grants Fast Track Designation for Alzheimer’s Treatment

[Healio](#) (5/3 Downey) reports that the FDA has granted fast track designation for Vaxxinity Inc.’s UB-311, an anti-amyloid beta immunotherapeutic vaccine, for the treatment of Alzheimer’s disease. UB-311 is an immunotherapeutic vaccine candidate, which targets toxic forms of amyloid beta in the brain, in order to treat Alzheimer’s disease. Phase 1, phase 2 and phase 2a long-term extension trials have shown UB-311 to be well-tolerated and safe in patients over 3 years of repeat dosing. FDA’s fast track program is designed to facilitate the development and expedite the review of new drugs intended to treat serious or life-threatening conditions. A fast track designation allows frequent engagement with the FDA, in order to discuss developmental plans and design of proposed clinical trials.

UB-312 Vaccine Well Tolerated by Healthy Adults in Ongoing Trial

[Parkinson’s News Today](#) (5/2, Wexler) reports, “UB-312, an experimental vaccine targeting aggregated and toxic forms of alpha-synuclein to treat Parkinson’s disease, was generally well tolerated at multiple doses in a clinical trial in healthy adults,” and appears also to have “prompted an immune response, as designed, against the alpha-synuclein protein.” The [findings](#) of the 50-patient phase 1 study were published online in the journal *Movement Disorders*.

FDA Approves Oral Treatment for Adults with ADHD

[Healio](#) (5/2, Herpen) reports that Supernus Pharmaceuticals announced FDA approval of viloxazine extended-release capsules (Qelbree) to treat ADHD in patients aged 18 years and older. Viloxazine, a norepinephrine reuptake inhibitor, was approved by the FDA in April 2021 to treat ADHD in children between the ages of 6 and 17.

FDA Could Remove Fast-Tracked Drugs Without Demonstrated Clinical Benefit

[Bloomberg Law](#) (5/4, Castronuovo, Baumann, Subscription Publication) reports, "The FDA could remove from the market any drugs that obtained accelerated approval if they fail to show a clinical benefit under a proposed package reauthorizing must-pass user fee legislation." Bipartisan leaders of the House Energy and Commerce Committee on Wednesday unveiled the proposal, which "would push sponsors of drugs approved through the accelerated pathway to complete required postmarket studies."

[Crediblemeds](#) (Woosley 5/26) Reports that "Deutetrabenazine (used to treat tardive dyskinesia) and Dexmedetomidine (a sedative) were removed from the Possible Risk of TdP category and are no longer on the QTdrugs list. Our analysis of new evidence did not support their continued placement on the list."

FDA Advisory Panel Rejects Pimavanserin For Treatment Of Alzheimer's Disease Psychosis

[MedPage Today](#) (6/17, Monaco) reported "An FDA advisory panel rejected pimavanserin (Nuplazid) for the treatment of hallucinations and delusions in patients with Alzheimer's disease psychosis on Friday." The Psychopharmacologic Drugs Advisory Committee "decided against recommending the drug for approval for these patients, citing a slew of shortcomings in supporting trial data." [Healio](#) (6/20, Herpen) reported "The Psychopharmacologic Drugs Advisory Committee (PDAC) voted nine to three that evidence presented did not support a conclusion that Nuplazid (pimavanserin, Acadia) is effective for the treatment of hallucinations and delusions in those with Alzheimer's."

House Passes Legislation Eliminating the X-Waiver

ASHP Government Relations (6/23) reported that "Today, the United States House of Representatives passed the Restoring Hope for Mental Health and Well-Being Act of 2022 ([H.R. 7666](#)), which included the ASHP-supported Mainstreaming Addiction Treatment Act. The legislation would eliminate the need for clinicians to apply for an X-waiver from the Substance Abuse and Mental Health Services Administration (SAMHSA) to administer medications for opioid use disorder (MOUD). Under the new law, clinicians would still be required to complete eight hours of training but would not need to apply for a separate waiver. This removes a major barrier for pharmacists, who were previously ineligible for X-waivers, regardless of education...The bill will now advance to the Senate for consideration."

FDA approves NDA to determine safety, efficacy of psilocybin for OCD treatment

[Healio](#) (6/27) The FDA has approved an investigational new drug application from Ceruvia Lifesciences to conduct a phase 2 clinical trial to determine the safety and efficacy of synthetic psilocybin for the treatment of obsessive-compulsive disorder. The clinical trial will be a multicenter, randomized, double-blind, active placebo-controlled trial that will examine the safety and efficacy of synthetic psilocybin for the treatment of OCD symptoms. The company said 105 participants will receive either 25 mg of SYN-101 (synthetic psilocybin) or active placebo. The primary endpoint of the trial is to determine the reduction of OCD symptoms for up to 12 weeks after a single dose of SYN-101.

Open Forum

Next Meeting Date

The next meeting is scheduled for October 28, 2022.

Adjourn

There being no further business, the meeting was adjourned at 1:35 p.m.

Approved: *David Moron*

David Moron, MD, Chairman

Minutes Prepared by:

Tonya Barrios, PhTR

Reviewed by:

Jean Baemayr, PharmD

Appendix A

Dulaglutide (Trulicity®)

Classification

Antidiabetic Agent

Pharmacology

Dulaglutide is a human GLP-1 receptor agonist (incretin mimetic) with 90% amino acid sequence homology to endogenous human GLP-1. Dulaglutide activates the GLP-1 receptor in pancreatic beta cells leading to glucose-dependent insulin release. It also decreases glucagon secretion, slows gastric emptying, and promotes satiety.

Indication

- Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- Reduce the risk of major adverse cardiovascular events (MACE) in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors

Black Box Warning

Risk of Thyroid C-Cell Tumors

In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans.

Trulicity is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC with use of Trulicity and inform them of symptoms of thyroid tumors (e.g., mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Trulicity.

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	Tmax = 24-72 h. Site of SC admin (abdomen, upper arm, thigh) had no significant effect on exposure to dulaglutide
Distribution	Mean central = 3.09 L, mean peripheral = 5.98 L

Pharmacokinetic Parameter	Details
Metabolism	Endogenously metabolized by dipeptidyl peptidase IV (DPP-IV) and endogenous endopeptidases. Metabolism occurs more slowly compared to endogenous GLP-1
Excretion	Half life = 5 days

Dosage/Administration

Recommended starting dose is 0.75 mg SC once weekly. Increase to 1.5 mg once weekly for additional glycemic control. If additional glycemic control is needed after at least 4 weeks on the 1.5 mg dose, increase to 3 mg once weekly. If additional glycemic control is needed after at least 4 weeks on the 3 mg dose, increase to the max dose of 4.5 mg once weekly.

- Administer once weekly, any time of day, with or without food
- Inject SC in the abdomen, thigh, or upper arm
- Rotate injection sites with each dose
- Inspect before use. Should be clear and colorless. Do not use if particulate matter or coloration is seen
- When using with insulin, administer as separate injections and never mix. Both can be injected in the same body region, but not adjacent to each other

Use in Special Population

Pregnancy

Risk Summary

Limited data with TRULICITY in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. There are clinical considerations regarding the risks of poorly controlled diabetes in pregnancy. Based on animal reproduction studies, there may be risks to the fetus from exposure to dulaglutide during pregnancy. TRULICITY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant rats administered dulaglutide during organogenesis, early embryonic deaths, fetal growth reductions, and fetal abnormalities occurred at systemic exposures at least 6-times human exposure at the maximum recommended human dose (MRHD) of 4.5 mg/week. In pregnant rabbits administered dulaglutide during organogenesis, major fetal abnormalities occurred at 5-times human exposure at the MRHD. Adverse embryo/fetal effects in animals occurred in association with decreased maternal weight and food consumption attributed to the pharmacology of dulaglutide.

The estimated background risk of major birth defects is 6–10% in women with pre-gestational diabetes with an HbA1c >7% and has been reported to be as high as 20–25% in women with an HbA1c >10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia-related morbidity.

Lactation

Risk Summary

There are no data on the presence of dulaglutide in human milk, the effects on the breastfed infant, or the effects on milk production. The presence of dulaglutide in milk of treated lactating animals was not determined. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRULICITY and any potential adverse effects on the breastfed infant from TRULICITY or from the underlying maternal condition.

Pediatric Use

Safety and effectiveness of Trulicity have not been established in pediatric patients. Trulicity is not recommended for use in pediatric patients < 18 years.

Geriatric Use

In the glycemic control trials, 620 (18.6%) TRULICITY-treated patients were 65 years of age or older and 65 (1.9%) TRULICITY-treated patients were 75 years of age or older at baseline. In the TRULICITY 1.5 mg treatment arm of the REWIND trial, a total of 2619 (52.9%) patients were 65 years of age or older, and 484 (9.8%) patients were 75 years of age or older at baseline.

No overall differences in safety or efficacy were detected between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment

TRULICITY has been studied in patients with varying degrees of renal function, including a dedicated study in patients with moderate to severe chronic kidney disease. No overall differences in safety or effectiveness were observed in these studies according to renal function.

In a clinical pharmacology study in subjects with renal impairment, including end-stage renal disease (ESRD), no clinically relevant change in dulaglutide pharmacokinetics (PK) was observed. In the 52-week study in patients with type 2 diabetes and moderate to severe renal impairment, the PK behavior of TRULICITY 0.75 mg and 1.5 mg once weekly was similar to that demonstrated in previous clinical studies.

No dose adjustment is recommended in patients with renal impairment including end-stage renal disease (ESRD). Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. Use TRULICITY with caution in patients with ESRD.

Hepatic Impairment

In a clinical pharmacology study in subjects with varying degrees of hepatic impairment, no clinically relevant change in dulaglutide PK was observed. However, there is limited clinical experience in patients with mild, moderate, or severe hepatic impairment; therefore, use TRULICITY with caution in these patient populations.

Gastroparesis

Dulaglutide slows gastric emptying. TRULICITY has not been studied in patients with preexisting gastroparesis. Use TRULICITY with caution in patients with gastroparesis.

Contraindication

Personal or family history of medullary thyroid carcinoma (MTC) or patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)

Prior serious hypersensitivity reaction to dulaglutide or to any of the product components. Serious hypersensitivity reactions including anaphylactic reactions and angioedema have been reported.

Precautions

Risk of Thyroid C-cell Tumors

In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. Glucagon-like peptide-1 (GLP-1) receptor agonists have induced thyroid C-cell adenomas and carcinomas in mice and rats at clinically relevant exposures. It is unknown whether TRULICITY will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human

relevance of dulaglutide-induced rodent thyroid C-cell tumors has not been determined.

One case of MTC was reported in a patient treated with TRULICITY in a clinical study. This patient had pretreatment calcitonin levels approximately 8 times the upper limit of normal (ULN). An additional case of C-cell hyperplasia with elevated calcitonin levels following treatment was reported in the cardiovascular outcomes trial (REWIND). Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans.

TRULICITY is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of TRULICITY and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with TRULICITY. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin values may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

Pancreatitis

In a pooled analysis from the original registration studies, 12 (3.4 cases per 1000 patient years) pancreatitis-related adverse reactions were reported in patients exposed to TRULICITY versus 3 in non-incretin comparators (2.7 cases per 1000 patient years). An analysis of adjudicated events revealed 5 cases of confirmed pancreatitis in patients exposed to TRULICITY (1.4 cases per 1000 patient years) versus 1 case in non-incretin comparators (0.88 cases per 1000 patient years).

Based on an analysis of adjudicated events in a clinical study evaluating Trulicity 1.5 mg, 3 mg, or 4.5 mg once weekly, pancreatitis occurred in 1 patient exposed to TRULICITY 1.5 mg (0.2%), in 2 patients exposed to TRULICITY 3 mg (0.3%), and 3 patients exposed to TRULICITY 4.5 mg (0.5%).

After initiation of TRULICITY, observe patients carefully for signs and symptoms of pancreatitis, including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting. If pancreatitis is suspected, promptly discontinue TRULICITY. If pancreatitis is confirmed, TRULICITY should not be restarted. TRULICITY has not been evaluated in patients with a prior

history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

Patients receiving TRULICITY in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia.

The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogue) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions including anaphylactic reactions and angioedema in patients treated with TRULICITY. If a hypersensitivity reaction occurs, discontinue TRULICITY; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity reaction to TRULICITY.

Anaphylaxis and angioedema have been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema or anaphylaxis with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to anaphylaxis with TRULICITY.

Acute Kidney Injury

In patients treated with GLP-1 receptor agonists, including TRULICITY, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events were reported in patients without known underlying renal disease. A majority of reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Because these reactions may worsen renal function, use caution when initiating or escalating doses of TRULICITY in patients with renal impairment. Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions.

Severe Gastrointestinal Disease

Use of Trulicity may be associated with gastrointestinal adverse reactions, sometimes severe. Trulicity has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.

Diabetic Retinopathy Complications in Patients with a History of Diabetic Retinopathy

In a cardiovascular outcomes trial with a median follow up of 5.4 years involving patients with type 2 diabetes with established cardiovascular disease or multiple cardiovascular risk factors, diabetic retinopathy complications occurred in patients treated with TRULICITY 1.5 mg (1.9%) and placebo (1.5%). These events were prospectively ascertained as a secondary composite endpoint. The proportion of patients with diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline (TRULICITY 8.5%, placebo 6.2%) than among patients without a known history of diabetic retinopathy (TRULICITY 1%, placebo 1%).

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

Adverse Effects

In clinical trials (up to 36 weeks) in patients on dulaglutide 1.5 mg to 4.5 mg, the most common adverse reactions were nausea (13.4-16.4%), diarrhea (7.0-11.4%), vomiting (5.6-9.3%), and dyspepsia (2.8-5.0%).

Incidence (%) of Hypoglycemia in Placebo-Controlled Trials

Add-on to Metformin, 26 wk	Placebo	Trulicity 0.75 mg	Trulicity 1.5 mg
Number of patients	N = 177	N = 302	N = 304
Hypoglycemia w/ glucose level < 54 mg/dL	0	0.3	0.7

Add-on to Metformin + Pioglitazone, 26 wk	Placebo	Trulicity 0.75 mg	Trulicity 1.5 mg
Number of patients	N = 141	N = 280	N = 279
Hypoglycemia with a glucose level < 54 mg/dL	1.4	2.1	0

Add-on to Glimepiride, 24 wk	Placebo	Trulicity 0.75 mg	Trulicity 1.5 mg
Number of patients	N = 60	n/a	N = 239

Add-on to Glimepiride, 24 wk	Placebo	Trulicity 0.75 mg	Trulicity 1.5 mg
Hypoglycemia with a glucose level < 54 mg/dL	0	n/a	3.3

In Combin. With Insulin Glargine ±Metformin, 28 wk	Placebo	Trulicity 0.75 mg	Trulicity 1.5 mg
Number of patients	N = 150	n/a	N = 150
Hypoglycemia with a glucose level < 54 mg/dL	9.3	n/a	14.7

Add-on to SGLT2i ± Metformin, 24 wk	Placebo	Trulicity 0.75 mg	Trulicity 1.5 mg
Number of patients	N = 140	N = 141	N = 142
Hypoglycemia with a glucose level < 54 mg/dL	0.7	0.7	0.7

Monitoring

Plasma glucose; HbA1c; renal function (in patients reporting severe GI reactions); signs/symptoms of pancreatitis; worsening diabetic retinopathy (in patients with a prior history).

Interactions

Oral Medications

TRULICITY delays gastric emptying and thus has the potential to reduce the rate of absorption of concomitantly administered oral medications. The delay in gastric emptying is dose-dependent but is attenuated with the recommended dose escalation to higher doses of TRULICITY. The delay is largest after the first dose and diminishes with subsequent doses. In clinical pharmacology studies, TRULICITY 1.5 mg did not affect the absorption of the tested orally administered medications to a clinically relevant degree. There is limited experience with the use of concomitant medications in clinical trials with TRULICITY doses of 3 mg and 4.5 mg.

Monitor drug levels of oral medications with a narrow therapeutic index (e.g., warfarin) when concomitantly administered with TRULICITY.

Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When initiating TRULICITY, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia.

Efficacy

Rewind

REWIND was a multicenter, randomized, double-blind, placebo-controlled trial performed at 371 sites in 24 countries. Men and women (≥ 50 years) with established or newly diagnosed diabetes ($\text{HbA1c} \leq 9.5\%$, no lower limit) on stable doses of up to two diabetes meds with or without basal insulin could participate if $\text{BMI} \geq 23 \text{ kg/m}^2$. Patients ≥ 50 yo were required to have vascular disease (previous mi, ischemic stroke, revascularization, hospitalization for unstable angina, imaging evidence of myocardial ischemia). Patients ≥ 55 yo were required to have myocardial ischemia; coronary, carotid, or lower extremity artery stenosis exceeding 50%; left ventricular hypertrophy; estimated $\text{gfr} < 60 \text{ ml/min}$; or albuminuria. Patients ≥ 60 yo had to have at least two of tobacco use, dyslipidemia, hypertension, or abdominal obesity. Exclusion criteria included $\text{eGFR} < 15 \text{ ml/min}$, cancer in the previous five years, severe hypoglycemia in the previous year, life expectancy < 1 year, coronary or cerebrovascular event within the previous 2 months, plans for revascularization.

9901 individuals were randomly assigned to treatment group (dulaglutide, $n = 4949$; placebo, $n = 4952$). Mean age was 66.2 years (SD 6.5) and 46.3% were female. 31.5% of participants had previous cardiovascular disease and 22.2% had a baseline $\text{eGFR} < 60 \text{ ml/min}$. The median duration of diabetes was 9.5 years (IQR 5.5-14.5) and the median HBA1c was 7.2% (IQR 6.6-8.1). Median eGFR was 74.9 ml/min .

Median follow-up was 5.4 years (IQR 5.1-5.9). Current guidelines were used to manage blood pressure, lipids, and other cardiovascular risk factors. Investigators were free to add any glucose-lowering drug apart from another glp-1 receptor agonist or pramlintide.

The primary outcome was the first occurrence of any component of the composite outcome (non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular causes or unknown causes). The primary outcome occurred in 12.0% of participants taking dulaglutide versus 13.4% of participants taking placebo (HR 0.88, 95% CI 0.79-0.99, $p = 0.026$). Across the three components of the primary outcome, greatest treatment benefit was seen in the number of non-fatal strokes (HR 0.76, 95% CI 0.61-0.95, $p = 0.017$). Subgroup analysis showed that hazard ratios were similar for participants with and without previous cardiovascular disease, individuals with $\text{HbA1c} < 7.2\%$ or $\geq 7.2\%$ and in individuals analyzed by age, sex, duration of diabetes, and BMI.

One of the secondary outcomes was a composite microvascular outcome comprised of eye (diabetic retinopathy) or renal outcomes. Renal outcomes included development of urinary albumin-to-creatinine ratio > 300 mg/g, sustained \geq 30% decline in eGFR (based on 2 consecutive eGFR concentrations), chronic renal replacement therapy. The incidence of the composite microvascular outcome was lower in patients taking dulaglutide than in those taking placebo (HR 0.87, 95% CI 0.79-0.95). The difference was driven by the occurrence of fewer composite renal outcomes in the dulaglutide versus the placebo group (HR 0.85, 95% CI 0.77-0.93). Dulaglutide did not significantly affect the incidence of all-cause mortality, heart failure, revascularization, hospital admission for unstable angina.

Compared with patients in the placebo group, patients taking dulaglutide had a 0.61% (95% CI 0.58-0.65) lower HbA1c ($p < 0.0001$), 1.46 kg (1.25-1.67) lower bodyweight ($p < 0.0001$), and a 1.70 mm Hg (1.33-2.07) lower systolic blood pressure ($p < 0.0001$).

Dulaglutide was well tolerated; serious adverse events did not differ significantly between groups. However, 47.4% of participants assigned to dulaglutide reported a gastrointestinal adverse event compared with 34.1% of participants assigned to placebo ($p < 0.0001$). 9.1% of participants taking dulaglutide and 6.3% of participants taking placebo stopped study drug because of an adverse event.

SUSTAIN 7

Weekly semaglutide (Ozempic) was compared to weekly dulaglutide (Trulicity) in an open-label, phase 3b, multi-center trial conducted in 1,201 adults with inadequately controlled type 2 diabetes (HbA1c 7.0-10.5%). Patients had been on at least 1500 mg per day of metformin monotherapy for 90 days before screening and were randomized to 40 weeks of SQ once a week treatment with low doses (semaglutide 0.5 mg vs dulaglutide 0.75 mg) and high doses (semaglutide 1.0 mg vs dulaglutide 1.5 mg.). Key exclusion criteria included history of pancreatitis, heart failure (New York Heart Association Class IV), CKD stage 3 and higher, proliferative retinopathy or maculopathy requiring acute treatment.

The primary endpoint was mean percentage HbA1c reduction from baseline to week 40. Mean HbA1c was reduced 1.5 (SE 0.06) percentage points with semaglutide 0.5 mg versus 1.1 (0.05) percentage points with dulaglutide 0.75 mg. At the higher doses, mean HbA1c was reduced 1.8 (SE 0.06) percentage points with semaglutide 1.0 mg versus 1.4 (SE 0.06) percentage points with dulaglutide 1.5 mg. Both estimated treatment differences were statistically significant ($p < 0.0001$)

The secondary endpoint was change from baseline to week 40 in bodyweight. At week 40, mean body weight was reduced by 4.6 kg (SE 0.28) with semaglutide 0.5 mg versus 2.3 kg (0.27) with dulaglutide 0.75 mg (treatment difference -2.26 (95% CI -3.02 to -1.51, $p < 0.001$). At the higher doses, mean body weight was reduced

by 6.5 kg (0.28) with semaglutide 1.0 mg versus 3.0 kg (0.27) with dulaglutide 1.5 mg (-3.55 kg [-4.32 to -2.78]; $p < 0.0001$).

GI disorders were the most frequently reported adverse event, occurring in 43% of patients receiving semaglutide 0.5 mg, 44% of patients receiving semaglutide 1.0 mg, 33% of patients receiving dulaglutide 0.75 mg and 48% of patients receiving dulaglutide 1.5 mg. Most of the adverse events that led to premature treatment discontinuation were gastrointestinal side effects that occurred early in the trial. Rates of treatment discontinuation were 8% in the semaglutide 0.5 mg group, 10% in the semaglutide 1.0 mg group, 5% in the dulaglutide 0.75 mg group, and 7% in the dulaglutide 1.5 mg group.

Dosage Forms/Cost

Single-dose pen (includes needles): 0.75 mg/0.5 ml, 1.5 mg/0.5 ml, 3 mg/0.5 ml, 4.5 mg/0.5 ml:

Per GoodRx, month supply of each strength is \$771.44

Special Considerations

SH, SSLC GLP-1 agonist purchases 9/1/21-2/28/22

Medication purchased	Units Purchased
Byetta (exenatide)	11
Bydureon (exenatide extended-release)	4
Victoza (liraglutide) prefilled pen	105
Saxenda (liraglutide) prefilled pen	30
Trulicity pen (dulaglutide)	300
Ozempic (semaglutide)	13
Wegovy (semaglutide)	6
Rybelsus (semaglutide) tablets	390

Summary/Conclusion

In 2019, liraglutide (Victoza) was the first glp-1 agonist added to the formulary. Liraglutide was chosen because, at the time, it was the most widely used glp-1 receptor agonist in the state system and the only glp-1 agonist approved to reduce CV risk in patients with established CV disease. It had also shown efficacy in the treatment of metabolic disturbances in patients treated with antipsychotics.

In 2020, semaglutide sc (Ozempic) and dulaglutide (Trulicity) were both approved to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes. Semaglutide sc (Ozempic) is approved to reduce MACE in adults with type 2 diabetes and established cardiovascular disease; dulaglutide (Trulicity) is approved to reduce MACE in adults with type 2 diabetes who have established cardiovascular disease or multiple cardiovascular risk factors. For the composite outcome of cv death, nonfatal MI, and nonfatal stroke, oral semaglutide (Rybelsus) demonstrated non-inferiority to placebo in a pre-approval trial designed to rule out an unacceptable increase in CV risk. The cv effects of oral semaglutide will be further tested in a large, longer term outcomes trial.

Per ADA 2022, glucagon-like peptide 1 receptor agonists with proven CVD benefit (with or without metformin) are appropriate initial therapy for individuals with type 2 diabetes with or at high risk for ASCVD. Along with SGLT2i with proven CVD benefit, GLP-1 RA's are also an appropriate first line choice for CV risk reduction in diabetic patients with CKD without albuminuria. GLP-1 RA's have improved secondary renal end points in CVOTs but their effects on hard renal outcomes are not as well established as those of the SGLT2i. They are listed as an alternative therapy for diabetic patients with CKD and albuminuria (≥ 200 mg/g creatinine) if SGLT2i are not tolerated or contraindicated. If injectable therapy is needed to reduce A1c, ADA 2022 also recommends GLP-1 RA over insulin, when possible.

Recommendation

Dulaglutide (Trulicity) should be added to the formulary.

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July 8, 2022