HHSC Psychiatric Executive Formulary Committee Minutes

The HHSC Psychiatric Executive Formulary Committee (PEFC) convened on October 25, 2019 in Room 125 - ASH Building 552. The meeting was called to order by Dr. Messer, Chair at 9:36 a.m.

<table>
<thead>
<tr>
<th>Members</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Jean Baemayr, PharmD- Secretary</td>
<td>Present</td>
<td>Vacant- local authority practitioner</td>
</tr>
<tr>
<td>John Bennett, M.D.</td>
<td>Present</td>
<td>Vacant- local authority practitioner</td>
</tr>
<tr>
<td>Bonnie Burroughs, RPh</td>
<td>Present</td>
<td>Tim Bray (non-voting)</td>
</tr>
<tr>
<td>Barbara Carroll, RN</td>
<td>Absent</td>
<td>Brad Fitzwater, M.D. (non-voting)</td>
</tr>
<tr>
<td>Ramona Gaston-McNutt, RN</td>
<td>Absent</td>
<td>Connie Horton, RNP (non-voting)</td>
</tr>
<tr>
<td>Catherine Hall, PharmD</td>
<td>Present</td>
<td>Raul Luna, RN, MSN (non-voting)</td>
</tr>
<tr>
<td>Jeanna Heidel, PharmD</td>
<td>Present</td>
<td>Mike Maples (non-voting)</td>
</tr>
<tr>
<td>Jeff Matthews, MD</td>
<td>Absent</td>
<td>Nina Muse, M.D. (non-voting)</td>
</tr>
<tr>
<td>Mark Messer, DO- Chair</td>
<td>Present</td>
<td>Peggy Perry (non-voting)</td>
</tr>
<tr>
<td>David Moron, MD</td>
<td>Present</td>
<td>Rachel Samsel, (non-voting)</td>
</tr>
<tr>
<td>Kenda Pittman, PharmD</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>Rishi Sawhney, MD</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>Glenn Shipley, DO</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>Ashton Wickramasinghe, MD</td>
<td>Absent</td>
<td></td>
</tr>
</tbody>
</table>

Guests Present: Ann Richards, PharmD, Central Administration, State Hospitals; Kasey Pena, PharmD, Clinical Pharmacist Austin State Hospital

Introduction and Other Information

Dr. Messer welcomed the committee members.

Dr. Murry has taken a position at Austin State Hospital and thus has resigned from his committee position as a physician representative for the state supported living centers.
Conflict of Interest
The committee members present did not reveal any issues with conflict of interest.

Review of Minutes of August 2, 2019
On a motion by Dr. Moron, seconded by Dr. Messer, the minutes of the August 2, 2019 meeting were approved as previously distributed.

Unfinished Business

TAC Title 25, Part 1, Chapter 415, Subchapter C  
(April 2017)
A draft of the revised TAC as prepared by the workgroup assigned to this committee in August is under review by the legal department. Once this review is completed, the draft will again be reviewed by the workgroup and then presented to the committee for approval. Once approved by the committee, the document will be submitted to the Rules Coordination Office for further processing.

Psychotropic Medication Utilization Parameters for Adults (August 2019)
The workgroup has not yet met.

New Business

Adverse Drug Reaction Reports
The committee discussed three adverse drug reaction reports that were received from the field. All three adverse events were reported to the FDA’s MedWatch program.

ADR: paliperidone/hyperprolactinemia
A 26-year-old Hispanic female was admitted to a state hospital on 03/07/2019. On admission she voiced feelings of self-harm, and was noted to be calm with a high pitched voice but garbled speech. Thought blocking and manic symptoms were also noted. She has a history of response to lithium and paliperidone and hence those medications were initiated on admission. Specifically, paliperidone 6 mg was initiated on day 5 of hospitalization and titrated to maximum dose of 12 mg daily by day 30 of hospitalization. Given the patient’s history of medication non-adherence it was decided to transition from oral paliperidone to its LAI (long-acting injection) formulation, Invega Sustenna. The patient received the first loading dose on day 34 of admission and the second loading dose was given 7 days later, followed by the first maintenance dose of 154 mg given on day 69 of admission and the second maintenance dose given 4 weeks later. The patient requested a
pregnancy test on day 97 of admission because of “not having my period since mid-April.” Consequently, a prolactin level was obtained on day 98 of hospitalization and results showed an elevation in level at 150.5 ng/mL (normal range 2.8-29.2 ng/mL) and a serum pregnancy test obtained that day was negative. Upon receipt and review of results, the attending discontinued the Invega Sustenna and referred the patient for evaluation by OB/GYN in the medical clinic to rule out medical causes considering that leading up to her complaint she had reported headaches and dizziness. Upon evaluation by facility OB/GYN, the patient reported to him amenorrhea and galactorrhea. An MRI of the brain with and without contrast was ordered to help rule out medical causes. The MRI was completed on day 107 of admission and showed “no pituitary enlargement, penial region abnormality or tonsillar ectopia. Negative pre and post contrast MRI of the brain, sella and pituitary gland. No pituitary microadenoma is seen at this time.” Given that MRI findings were negative, the treatment team determined that the prolactin elevation was secondary to paliperidone use. The medication was not re-started. A repeat prolactin level was ordered for a month post initial elevation; however, the patient refused a lab draw.

Medications administered within 24 hours of identified prolactin elevation include: nicotine gum 2 mg (total of 12 pieces), milk of magnesia, lithium 450 mg twice daily, Invega Sustenna 156 mg IM, hydroxyzine twice daily PRN (2 doses).

Aripiprazole was ordered to be initiated at the time of next scheduled Invega Sustenna injection on 07/09/2019, with prolactin level also scheduled to be rechecked.

Antipsychotics are implicated in hyperprolactinemia by way of dopamine blockade in the tuberoinfundibular pathway of the hypothalamus. Antipsychotics with higher affinity for dopamine receptors present with higher risk of prolactin elevations in men and women. Examples of such antipsychotics include but are not limited to haloperidol, risperidone and paliperidone. Seventy percent of patients with schizophrenia experience prolactin elevation. Per HHSC antipsychotic monitoring guidelines, prolactin levels are only obtained when patients are symptomatic and are not part of the routine monitoring for antipsychotics. Some formulations of LAI antipsychotics are associated with greater prolactin levels and related side effects, compared to their oral counterpart. Cessation of oral antipsychotics typically results in normalization of prolactin within 2–3 weeks; however, prolactin can remain above pre-treatment values for 6 months or longer after discontinuation of some LAIs [Psychopharmacology 2017; 234:3279–3297]. In our patient, a baseline prolactin level was not on file, and she had previously taken oral paliperidone with no known adverse effects. This is the first time she received long acting Invega Sustenna at our facility. Given the timeline of events, and the negative results of the MRI, the prolactin elevation is related to paliperidone use. She has started taking aripiprazole. The patient has not resumed menstruation, but the reported galactorrhea has abated.
6 weeks after initial prolactin elevation identified, the patient agreed to a repeat lab, and her prolactin had dropped to 89.1 ng/mL.

**ADR: ferrous sulfate/chemical gastritis**

A 64-year-old male was admitted to a state psychiatric hospital in January of 2019. Diagnoses include major depressive disorder, substance use disorder, unspecified anxiety disorder and medical conditions of hypertension, cardiovascular disease post stent placement, COPD, type 2 diabetes, and hyperlipidemia. During the admission he was transferred to a medical hospital after reporting chest pain. While admitted he was found to have significantly reduced hemoglobin (Hgb) at 6.4 g/dL, which had been 8.7 g/dL and 10.8 g/dL on two prior CBCs, at admission and at 1 month after admission, respectively. He had a positive fecal occult blood and was administered packed red blood cells (PRBC). An esophagogastroduodenoscopy (EGD) was performed and he was diagnosed with H. Pylori infection and several ulcers were cauterized. Hgb was 8.4 g/dL on return. Aspirin 81 mg was continued but ticagrelor was discontinued until follow-up with cardiology. An H. Pylori treatment regimen was prescribed and completed. A month after returning from the medical hospital the Hgb was 9.2 g/dL, hematocrit (Hct) 29% and RBC 3.64 10¹²/L. A follow-up EGD and biopsy was recommended 4-6 weeks later and was performed approximately 6 weeks after return from the medical hospital. The prescribed regimen at the time was zolpidem 10 mg at bedtime, simethicone 80 mg four times daily, sennosides and docusate sodium 8.6 mg-50 mg, Miralax 17 grams daily, pantoprazole 40 mg twice daily, metoprolol 25 mg daily, metformin 500 mg in the morning, melatonin 9 mg at bedtime, isosorbide dinitrate 5 mg twice daily, insulin aspart sliding scale and insulin glargine, gabapentin 100 mg three times daily and 200 mg at bedtime, fluoxetine 40 mg daily, donepezil 10 mg daily, buspirone 5 mg three times daily, baclofen 5 mg twice daily, atorvastatin 20 mg in the morning, allopurinol 300 mg in the morning, and ferrous sulfate 325 mg twice daily. Of note, the ferrous sulfate was prescribed at admission in January. The repeat EGD noted mild gastritis with patchy erythema in the mid stomach. No H. pylori or peptic ulcer disease seen and ulcers appeared to have healed completely. The biopsy of the stomach showed erosive and ulcerative reactive gastropathy (chemical gastritis) with associated brown crystalline pigment, most consistent with iron pill gastritis. Sections showed markedly edematous gastric mucosa with evidence of superficial mucin loss with associated regenerative epithelial changes. Superficial disrupted gastric foveolar epithelium present admixed with brown crystalline material and neutrophils, most consistent with iron pigment. Due to the EGD and biopsy results, ferrous sulfate was discontinued. A month and a half after discontinuation of ferrous sulfate the Hgb was 11.1 g/dL, Hct 35.2%, and RBC 4.49 g/dL.

Iron pill-induced chemical gastritis is a rare but potentially serious ADR from iron pill ingestion. Iron pill-induced gastritis causes corrosive mucosal injury similar to that caused by chemical burns. Cases have been reported in the literature including
a similar case of a 59-year-old male with iron deficiency anemia on ferrous sulfate tablets who underwent an upper endoscopy. A superficial gastric ulceration in the body was noted and biopsies revealed heavy iron deposition confirming the ulceration was a consequence of the iron tablets [ACG Case Rep J. 2013 Oct 8;1(1):13-5].

**ADR: olanzapine/prolonged QTc**

A 45-year-old Hispanic female admitted to a state hospital on 07/26/2019. She was noted to be calm and cooperative during admission interview. Her thought process and content were tangential and disorganized. She reported a history of illicit drug use including cannabis, LSD, cocaine, and occasional alcohol. On admission, her EKG showed a QTc of 437 msec and “sinus rhythm leftward axis nonspecific T abnormality.” Upon admission her valproate level was low at 58.3 mcg/mL, her urine drug screen was negative, and all other labs were unremarkable.

Prior to arrival, she was prescribed aripiprazole, benzotropine, and divalproex ER. Benztropine 1 mg and divalproex ER 1000 mg were continued upon admission, but aripiprazole was not restarted until two days later. On 7/29/19 olanzapine 10 mg at bedtime was ordered to better manage her psychosis and mood and she was given her first dose later that day. Upon initiation of olanzapine, her aripiprazole was discontinued. She took olanzapine, benzotropine, and divalproex ER for the next seven days. On day 11 (8/5/19) an EKG was performed to follow up on the T abnormality seen on the EKG from 7/26; the follow up EKG showed “sinus rhythm leftward axis otherwise normal” and an increased QTc of 460 msec, increased 23 msec from baseline. Another follow up EKG was ordered for the next week to confirm the prolonged QTc results were accurate. On 8/6/19, olanzapine 5 mg every morning was added to her regimen, totaling 15 mg of olanzapine per day. Nine days later, on 8/15/19, she received her morning dose of olanzapine and went for the follow up EKG. The EKG showed a “T abnormality in anterior leads” and a QTc of 525 msec, significantly increased from baseline by 88 msec. Reportedly, a second EKG was done the same day to ensure accuracy and a similar result was obtained, though a copy was never scanned into the chart. Because of the steady increase in QTc throughout treatment with olanzapine, this ADR was believed to have been caused by her medication change. Olanzapine and benztropine were discontinued immediately. On 8/16/19, aripiprazole 15 mg every morning was re-initiated for management of her psychosis. Four days later (8/20/19), the patient’s EKG normalized and showed a QTc of 431 msec and “sinus rhythm leftward axis otherwise normal.”

Medications administered within 24 hours of identified QTc prolongation were: olanzapine 5 mg daily in the morning and 10 mg daily at bedtime, divalproex ER 1000 mg daily at bedtime (day 20), and benztropine 1 mg daily at bedtime (day 20).
Nearly all antipsychotics carry the risk of prolonging the QTc interval. Per the FDA, mean changes in QTc greater than 20 msec are associated with a high risk for cardiac arrhythmia. Additionally, the FDA sets “critical thresholds” at a QTc above 500 msec and a QTc which increases more than 60 msec over baseline; all of which were experienced in this case. A randomized evaluation analyzed the effects of six antipsychotic agents on QTc, olanzapine being one of them. All six antipsychotics had a mean increase in the QTc interval, with olanzapine having the least increase (Journal of Clinical Psychopharmacology, 2004;24:62-69). This data is supported by credible meds, which lists olanzapine under the category of “possible risk” for prolonging QTc and “conditional risk” for being associated with torsades de pointes (TdP) under certain conditions. Though olanzapine has low risk for prolonging the QTc interval, it is still possible, and the patient’s QTc was steadily increasing far from baseline throughout the continuation of olanzapine therapy. Aripiprazole is listed on credible meds as a medication which has “possible risk” to cause QTc prolongation, but lacks evidence to show a risk of TdP. A recent meta-analysis looked at the effects of seven second-generation antipsychotics (SGA) on QTc prolongation. The primary finding was that aripiprazole was the only SGA with a statistically significant lesser change in mean Bazett’s corrected QTc and lower risk to cause Bazett’s corrected QTc prolongation (Journal of Psychopharmacology, 2005;25:646-666). Given the data available on antipsychotics and QTc prolongation, the dramatic increase in the patient’s QTc with olanzapine, and her return to baseline with aripiprazole, it is highly likely olanzapine was the offending agent in this case.

Quick Reference for the Treatment of Acute Agitation

The committee reviewed an updated Quick Reference for the Treatment of Acute Agitation document.

On a motion by Dr. Moron, seconded by Dr. Messer, the committee approved the updated version with a few minor revisions. The revised document will be posted on the PEFC website.

OP 3-1 Anti-androgen Therapy for Aggression Triennial review

The committee reviewed recommended revisions to the anti-androgen therapy for aggression policy. The document will be sent to the legal department for review.

Heplisav-B system usage review

Heplisav-B was newly added to the formulary in October 2018. As this was a new product on the market at that time, state hospital and state supported living center Heplisav-B usage from October 1, 2018 through September 12, 2019 was reviewed. Purchases were $71,606 for the state hospitals and $32,511 for the state supported living centers. No adverse drug reactions or medication errors related to the use of Heplisav-B were reported from the state hospitals or state supported living centers.
Ketamine system usage review

Ketamine injection was newly added to the formulary in October 2018. As this was a new product for our facilities at that time, state hospital and state supported living center ketamine injection usage from October 1, 2018 through September 12, 2019 was reviewed. Purchases were $35 for the state hospitals and $96 for the state supported living centers. No adverse drug reactions or medication errors related to the use of ketamine injection were reported from the state hospitals or state supported living centers.

New Drug Applications

Conflict of Interest disclosure forms were received from all non-committee members who had submitted a new drug application and/or prepared a monograph. No conflicts were noted.

Cannabidiol (Epidiolex®) – presented by Dr. Burroughs.

Please refer to Appendix A for the monograph and application that were considered when determining action by the committee.

On a motion by Dr. Burroughs, seconded by Dr. Pittman, it was recommended to add cannabidiol to the formulary as a reserve agent with the following restriction for use:

1. To be used in patients with a diagnosis of Lennox-Gastaut syndrome or Dravet syndrome; and
2. Having treatment-resistant seizures after failed trials of adequate dose and duration of two other antiepileptic agents; and
3. When recommended by a neurologist.

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

Liraglutide (Victoza®) - presented by Dr. Hall

Please refer to Appendix B for the monograph and application that were considered when determining action by the committee.

On a motion by Dr. Messer, seconded by Dr. Heidel, it was recommended to add liraglutide (Victoza®) to the formulary. The formulary check list was completed and no issues were detected.

Solifenacin (Vesicare®) – presented by Dr. Baemayr

Please refer to Appendix C for the monograph and application that were considered when determining action by the committee.

On a motion by Dr. Bennett, seconded by Dr. Pittman, it was recommended to add solifenacin to the formulary. The formulary check list was completed and no issues were detected.
Hepatitis C Drug Purchases

For the fourth quarter of fiscal year 2019 (June 2019-August 2019), the following purchases for drugs to treat hepatitis C were made:

State Hospitals: $32,000
State Supported Living Centers: $0

Quarterly Non-Formulary Drug Justification Report

For the first through fourth quarters of fiscal year 2019, only the state hospitals reported use of non-formulary agents. The state supported living centers 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 fourth quarter of fiscal year 2019 (June 2019-August 2019):

- losartan (Cozaar®)- added at the August PEFC meeting.
- flaxseed oil
- clotrimazole-betamethasone dipropionate (Lotrisone®)- Dr. Hall presented a New Drug Addition request from SASH for this medication and will be presenting a monograph at a future meeting.
- acetaminophen-caffeine-butalbital (Fioricet®)
- apixaban (Eliquis®)

Drug Formulary Sectional Review:

In reviewing the formulary drug listings for Dermatologicals (Corticosteroids through Miscellaneous Dermatologicals), Irrigation, and Immunological products, Dr. Hall made the following recommendation:

- Influenza Virus Vaccine (Fluzone, Fluvirin)- remove brand names from formulary listings.

On a motion by Dr. Hall, seconded by Dr. Moron, the change recommended above was approved. The formulary will be updated.

Drug Deletions

The committee considered the recommendation to delete atovaquone, as purchases for the past two years have been limited to Texas Center for Infectious Disease.

On a motion by Dr. Heidel, seconded by Dr. Messer, the deletion of atovaquone from the formulary was approved. The formulary will be updated.
New Dosage Forms

The committee did not consider adding any additional products not already specified in the sectional review or new drug application review.

HHSC Psychiatric Drug Formulary Tables Annual Review

Psychotropic Dosage Guidelines

The committee reviewed proposed revisions to the psychotropic dosage guideline tables in the formulary:

Children and Adolescent Treatment of Behavioral Emergencies (Intramuscular short-acting agents):

- Delete aripiprazole (no longer available)
- Delete fluphenazine
- Updates to maximum single doses, minimum intervals, and maximum total doses per day
- Updates to references

Adult Treatment of Behavioral Emergencies (Intramuscular short-acting agents):

- Delete aripiprazole (no longer available)
- Change minimum interval for IM lorazepam to 0.5 hr
- Updates to references

Antipsychotics Suggested Maximum Doses

- Updates to adult, child, and adolescent dosing
- Add FDA approved aripiprazole dosing for Tourette’s
- Updates to foot notes

Antidepressants Suggested Maximum Doses

- Updates to child and adolescent dosing
- Add dosing for Obsessive-Compulsive Disorder

Mood Stabilizers Suggested Maximum Doses

- Updates to child and adolescent dosing
- Updates to therapeutic reference ranges

Stimulants Suggested Maximum Doses

- Updates to adult, child, and adolescent dosing

Miscellaneous Drugs Used for Psychotropic Purposes Recommended Doses

- Remove “Reserve Use” note from naltrexone tablets
• Add naltrexone microspheres (Vivitrol®) with the note of “Reserve Use”

Anxiolytics Suggested Maximum Doses
No recommended changes

Hypnotics Suggested Maximum Doses
• Updates to child and adolescent dosing
• Update to footnotes

On a motion by Dr. Moron, seconded by Dr. Heidel, the revisions to the tables were approved. The formulary will be updated with the approved changes.

Reserve Drugs.
The committee reviewed proposed revisions to reserve drug table in the formulary:
• Delete atovaquone (refer to Drug Deletions section of minutes)
• Add numbers (1-5) to items in guidelines for use of esketamine nasal spray (Spravato®)

On a motion by Dr. Heidel, seconded by Dr. Messer, the revisions to the table were approved. The formulary will be updated with the approved changes.

Therapeutic Serum Concentrations of Some Anticonvulsants.
The committee reviewed proposed revisions to the therapeutic serum concentration of anticonvulsants table in the formulary:
• Add lamotrigine
• Updates to listed Sources

On a motion by Dr. Bennett, seconded by Dr. Sawhney, the revisions to the table were approved. The formulary will be updated with the approved changes.

HHSC Psychiatric Drug Formulary
On a motion by Dr. Bennett, seconded by Dr. Messer, the 2020 HHSC Psychiatric Drug Formulary was approved with the revisions as approved at today’s committee meeting. The updated formulary will be posted on the PEFC website.

HHSC Antipsychotic Tier Schedule Annual Review
The committee reviewed proposed updates to the antipsychotic tier table.
• Add Initio (aripiprazole LAI)
• Add clozapine to Tier 2 (appears to have been inadvertently omitted at last review)
• Updates to pricing codes
On a motion by Dr. Messer, seconded by Dr. Bennett, the revisions to the table were approved. The updated table will be submitted for posting on the PEFC website.

**Dissemination of Committee Information**

The committee discussed how information from committee meeting was distributed. Minutes and updates to the formulary and reference documents are posted on the PEFC website. Minutes are also distributed by Dr. Baemayr via email to committee members, state hospital pharmacy directors, and state hospital medical directors. Dr. Pittman distributes to the state supported living centers. Dr. Sawhney will distribute to the Local Mental Health Authorities.

**Issues from the Medical Director, State Hospital System**

Dr. Muse was not available to present a report.

**Issues from the Medical Services Coordinator, State Supported Living Centers**

Dr. Shipley reported that the SSLC Psychiatric Coordinator position has been posted.

**FDA Drug Safety Communications and Recalls**

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

[08-28-2019] The Food and Drug Administration (FDA) has received reports that the use of Mavyret, Zepatier, or Vosevi to treat chronic hepatitis C in patients with moderate to severe liver impairment has resulted in rare cases of worsening liver function or liver failure. These medications are FDA-approved to treat chronic hepatitis C in patients without liver impairment or with mild liver impairment (Child-Pugh A). Clinical trials in patients with compensated cirrhosis or mild liver impairment (Child-Pugh A) have shown that these medicines are well tolerated and highly effective. These medications are not indicated for use in patients with moderate to severe liver impairment.

In many of the reported cases, liver failure occurred in patients who had signs and symptoms of moderate to severe liver impairment (Child-Pugh B or C) or other serious liver problems and should not have been treated with these medicines. In some cases, patients were reported to have no cirrhosis or compensated cirrhosis with mild liver impairment (Child-Pugh A) despite having evidence of decreased platelets at baseline or an increase in the pressure within the portal vein that carries blood from the digestive organs to the liver. In addition, some cases had other significant pre-existing risk factors such as liver cancer, alcohol abuse, or serious medical illnesses associated with serious liver problems. These factors may
have contributed to clinical worsening of liver function or liver failure during treatment with these hepatitis C medicines. In most cases, liver failure or decompensation typically occurred within the first 4 weeks of starting treatment. In most patients, symptoms resolved or new onset worsening of liver function improved after stopping the medicine.

[09-13-2019]: The FDA has learned that some ranitidine products contain a nitrosamine impurity called N-nitrosodimethylamine (NDMA).

The FDA has issued the following recalls that may affect our facilities:

**Ranitidine:** Apotex Corp. is voluntarily, on a precautionary basis, recalling ranitidine tablets to the retail level. Apotex has learned from the U.S. Food and Drug Administration and other Global regulators that some ranitidine medicines, including brand and generic formulations regardless of the manufacturer, contain NDMA at low levels. To date, Apotex has not received any reports of adverse events related to use of the product.

Sandoz Inc. is voluntarily recalling all quantities and lots within expiry of ranitidine in the US to the consumer level because of confirmed contamination with NDMA above levels established by the FDA. To date, Sandoz has not received any reports of adverse events related to use of the product as part of this recall.

**Losartan:** Torrent Pharmaceuticals Limited is expanding its recall to include an additional 3 lots of losartan and losartan /hydrochlorothiazide to the consumer level due to the detection of trace amounts of N-Methylnitrosobutyric acid (NMBA) found in finished batches manufactured utilizing active pharmaceutical ingredient (API) manufactured by Hetero Labs. Torrent is only recalling lots of losartan-containing products that contain NMBA above the acceptable daily intake levels released by the FDA.

*News Briefs*

The following information was shared with the committee members:

**FDA Approves Pitolisant for Excessive Daytime Sleepiness**

MedPage Today (8/15, George) reports the FDA approved Harmony Biosciences’ Wakix (pitolisant) for the treatment of excessive daytime sleepiness in adults with narcolepsy. The chief medical officer of Harmony said in a statement that the drug is the first FDA-approved treatment for patients with narcolepsy that is not classified as a controlled substance.

**FDA Expanding Investigation into US Generic Drug Impurities**
Reuters (8/28, Erman, Mishra) reports the FDA is expanding its investigation into impurities in US generic drugs beyond angiotensin II receptor blockers (ARBs). The FDA is testing samples of other medicines with similar manufacturing processes to those in which concerning impurities have been discovered.

**Experimental Alzheimer’s Disease Vaccine Appears Effective**

Reuters (9/9, Burger) reports Axon Neuroscience, a Slovakian biotech firm, announced that its experimental Alzheimer’s disease vaccine AADvac1 “showed early signs of efficacy in a mid-stage trial.” The vaccine is designed to prevent malformed tau proteins from spreading and sticking together in Alzheimer’s patients’ brains, keeping them from forming tangles that disrupt signaling between nerve cells.

**Jury Hits J&J with $8B Verdict In Risperdal Lawsuit**

The New York Times (10/8, Zaveri, Thomas) reports that on Tuesday, a Philadelphia jury hit Johnson & Johnson with an $8 billion verdict over its marketing of the anti-psychotic drug Risperdal, siding with a Maryland man who argued that the health care giant downplayed risks that the drug could lead to breast growth in boys. The suit accused J&J subsidiary Janssen of failing to warn doctors about Risperdal’s risks while improperly marketing it as a treatment for certain mental health disorders in children.

The Wall Street Journal (10/8, Loftus, Subscription Publication) reports that currently, this is the largest award out of the 13,000 lawsuits against the company alleging Risperdal caused gynecomastia in boys.

**FDA Approves Transdermal Patch Formulation of Asenapine**

Medscape (10/15, Subscription Publication) reports the FDA has approved a transdermal patch formulation of the atypical antipsychotic asenapine (Secuado, Noven Pharmaceuticals). The once-daily patch provides sustained concentrations of asenapine over 24 hours.

**Open Forum**

Dr. Sawhney asked if there were any available guidance documents for tapering benzodiazepines. If no references are readily available, this might be a future project for the committee. He also shared a link to SMIadvisor.org, a site with resources on serious mental illnesses for providers, clinicians, individuals, and families.

Dr. Hall offered to present a literature review of high-dose olanzapine use at the next committee meeting.

**Next Meeting Date**

The next meeting is scheduled for January 31, 2019.
Adjourn
There being no further business, the meeting was adjourned at 3:30 p.m.

Approved:  

Mark Messer, D.O.
Mark Messer, D.O., Chairman

Minutes Prepared by:
Jean Baemayr, PharmD

Appendix

- Appendix A – Cannabidiol (Epidiolex®) New Drug Application and monograph
- Appendix B – Liraglutide (Victoza®) New Drug Application and monograph
- Appendix C – Solifenacin (Vesicare®) New Drug Application and monograph
NEW DRUG APPLICATION FORM

For consideration of inclusion into the HHSC Psychiatric Drug Formulary

Date:_10-15-2019____________

Name of practitioner submitting the application:_Bonnie Burroughs____

Name of entity with which the practitioner is associated by employment or contract (i.e., state hospital, state supported living center, state center, or local authority (state-operated community services (SOCS) or community MHMR center)): __Requested by PEFC________________

Information regarding new drug:

<table>
<thead>
<tr>
<th>Therapeutic Classification</th>
<th>Anticonvulsant- cannabinoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic Name</td>
<td>cannabidiol</td>
</tr>
<tr>
<td>Trade Name(s)</td>
<td>Epidiolex®</td>
</tr>
<tr>
<td>Manufacturer(s)</td>
<td>Greenwich Biosciences</td>
</tr>
<tr>
<td>Dosage Form(s)</td>
<td>Oral solution</td>
</tr>
</tbody>
</table>

Explain the pharmacological action or use of this drug:
Indicated for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older.

Explain the advantages of this drug over those listed in the formulary:
Will offer an additional therapeutic choice for specific types of seizures not controlled by formulary medications.

State which drugs this new drug would replace or supplement:
Will supplement other anticonvulsants currently on formulary.

******************************************************************************

☐ application is approved ________n/a___________________________

signature of chairman of facility pharmacy and therapeutics committee

OR

☐ application is appropriate and complete_____n/a___________________________

signature of clinical/medical director or designee
Cannabidiol (Epidiolex®)

Classification:
Anticonvulsant—Cannabinoid [1,2].

Pharmacology:
The precise mechanisms by which Cannabidiol exerts its anticonvulsant effect in humans are unknown. It does not appear to have anticonvulsant effects through interaction with the cannabinoid receptors. [1,2].

Indications:
Lennox-Gastaut syndrome
Severe myoclonic epilepsy in infancy [1,2].

Pharmacokinetics:

Absorption:
Cannabidiol time to maximum plasma concentration of 2.5 to 5 hours at steady state. A high fat/high calorie increased Cmax by 5 fold and AUC by 4 fold.

Distribution:
The apparent volume of distribution in healthy volunteers was 20963 L to 42489 L. indicating high lipophilicity. Protein binding of the cannabidiol and its metabolites was >94% in vitro.

Metabolism:
Hepatic (primarily) and gut by CYP2C19, CYP3A4, UGT1A7, UGT1A9, and UGT2B7 to active metabolite 7-OH-CBD and then to inactive metabolite 7-COOH-CBD

Excretion:
Excreted in feces, with minor renal clearance. Based on twice-daily dosing for 7 days in healthy individuals, the elimination half-life ranges from 56 to 61 hours. [1,2].

Dosage and administration:
Lennox-Gastaut syndrome
Initial, 2.5 mg/kg orally twice daily for 1 week; then may increase to maintenance dosage of 5 mg/kg orally twice daily. If tolerated and further
seizure reduction is necessary, may increase in weekly increments of 2.5 mg/kg twice daily to MAX 10 mg/kg twice daily (20 mg/kg/day). If more rapid titration from 10 mg/kg/day to 20 mg/kg/day is warranted, the dosage may be increase no more frequently than every other day [1,2].

Discontinuing therapy, decrease dose gradually [1,2].

Severe myoclonic epilepsy in infancy

2 Years or Older

1) Initial dosage: 2.5 mg/kg orally twice daily for 1 week.

2) Dosage titration: May increase to maintenance dosage of 5 mg/kg orally twice daily after 1 week at initial dosage. If tolerated and further seizure reduction is necessary, may increase in weekly increments of 2.5 mg/kg twice daily to 10 mg/kg twice daily. If more rapid titration from 10 mg/kg/day to 20 mg/kg/day is warranted, the dosage may be increase no more frequently than every other day [1,2].

3) Maximum dosage: 20 mg/kg/day [1,2].

4) Discontinuing therapy: Decrease dose gradually. Avoid abrupt discontinuation to minimize risk of increased seizure frequency and status epilepticus [1,2].

Contraindications:

Hypersensitivity to cannabidiol or any of the components of the product, which includes sesame seed oil. [1,2].

Precautions:

Hepatic: Hepatocellular injury, including dose-related elevations of liver transaminases, have been reported with some cases associated with hospitalization. Increased risk in patients concomitantly taking valproate or clobazam and with elevated baseline transaminase levels; monitoring recommended. Therapy interruption or discontinuation may be necessary [1,2].

Immunologic: Hypersensitivity reactions have been reported and may require antihistamines; discontinue therapy if hypersensitivity reactions occur. [1,2]

Neurologic: Somnolence and sedation, including lethargy, has been reported; increased risk in patients concomitantly taking clobazam. Other central nervous system depressants, including alcohol, may potentiate effects; monitoring recommended [1,2]

Psychiatric: Increased incidences of suicidal behavior or ideation may occur; monitoring recommended. [1,2]

Withdrawal: Gradually withdraw therapy due to the risk of increased seizure frequency and status epilepticus. [1,2]
Adverse Reactions:

**Common**

**Dermatologic:** Rash (7% to 13%)

**Gastrointestinal:** Decrease in appetite (16% to 22%), Diarrhea (9% to 20%)

**Immunologic:** Infectious disease (40% to 41%)

**Neurologic:** Asthenia, Difficulty sleeping, Insomnia, Sleep disorder, Somnolence (23% to 25%)

**Other:** Fatigue, Malaise

**Serious**

**Hepatic:** Increased liver aminotransferase level (8% to 16%). Patients also taking valproate and/or clobazam were at increased risk for elevated transaminase levels.

**Psychiatric:** Suicidal behavior, Suicidal thoughts

**Respiratory:** Hypoxia, Respiratory failure [1,2]

Monitoring:

ALT, AST, and total bilirubin (baseline and 1, 3, and 6 months after initiation, followed by periodic monitoring as clinically indicated [eg, within 1 month of dose change or initiation of concomitant hepatotoxic drug or clinical signs or symptoms of hepatic dysfunction

Interactions:

Cilostazol: CYP2C19 Inhibitors may increase the serum concentration of Cilostazol. Management: Consider reducing the cilostazol dose to 50 mg twice daily in patients who are also receiving inhibitors of CYP2C19. *Risk D: Consider therapy modification*

Citalopram: CYP2C19 Inhibitors (Moderate) may increase the serum concentration of Citalopram. Management: Limit citalopram dose to a maximum of 20 mg/day if used with a moderate CYP2C19 inhibitor. Patients using this combination should be monitored closely for evidence of citalopram toxicity (e.g., serotonin syndrome, QT prolongation, etc.). *Risk D: Consider therapy modification*

CloBAZam: Cannabidiol may increase serum concentrations of the active metabolite(s) of CloBAZam. Cannabidiol may increase the serum concentration of CloBAZam. *Risk C: Monitor therapy*

Clopidogrel: CYP2C19 Inhibitors (Moderate) may decrease serum concentrations of the active metabolite(s) of Clopidogrel. Management: Due to a risk for impaired clopidogrel effectiveness with such a combination, carefully consider
the need for a moderate CYP2C19 inhibitor in patients receiving clopidogrel. Monitor patients closely for evidence of a diminished response to clopidogrel. *Risk D: Consider therapy modification*

**CNS Depressants:** Cannabidiol may enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

**CYP2C19 Inducers (Strong):** May decrease the serum concentration of Cannabidiol. *Risk C: Monitor therapy*

**CYP2C19 Inhibitors:** May increase the serum concentration of Cannabidiol. *Risk C: Monitor therapy*

**CYP2C19 Substrates (High risk with Inhibitors):** CYP2C19 Inhibitors (Moderate) may decrease the metabolism of CYP2C19 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

**CYP3A4 Inducers (Strong):** May decrease the serum concentration of Cannabidiol. *Risk C: Monitor therapy*

**CYP3A4 Inhibitors:** May increase the serum concentration of Cannabidiol. *Risk C: Monitor therapy*

**Flibanserin:** CYP2C19 Inhibitors (Moderate) may increase the serum concentration of Flibanserin. *Risk C: Monitor therapy*

**Valproate Products:** May enhance the hepatotoxic effect of Cannabidiol. *Risk C: Monitor therapy* [1,2]

**Efficacy:**

**Lennox-Gastaut syndrome**

“Study 1—Randomized, double-blind, placebo-controlled trial N=171 compared a dose of cannabidiol 20 mg/kg/day with placebo. 94% of patients were taking at least 2 concomitant AED’s. The most frequently used concomitant AED’s were clobazam (49%), valproate (40%), lamotrigine (37%) levetiracetam (34%) and rufinamide (27%).

Study 2—Randomized, double-blind, placebo-controlled trial N=225 compared a dose of 10 mg/kg/day dose and a 20 mg/kg/day dose of cannabidiol with placebo. 94% of patients were taking at least 2 concomitant AED’s. The most frequently used concomitant AED’s were clobazam (49%), valproate (38%), levetiracetam (31%), lamotrigine (30%) and rufinamide (29%). [3].

In 2 randomized trials of patients 2 to 55 years old with Lennox-Gastaut syndrome and seizures inadequately controlled with standard epileptic therapy, the addition of cannabidiol compared with the addition of placebo significantly reduced the percentage of drop seizures from baseline to 14 weeks. In Study 1 (N=171), cannabidiol 20 mg/kg/day reduced the percentage of drop seizures/28 days by 44% compared with a 22% reduction with placebo. In Study 2 (N=225), cannabidiol 10 mg/kg/day reduced the percentage of drop seizures/28 days by 37%, and cannabidiol 20 mg/kg/day reduced the percentage by 42% compared with a 17% reduction with placebo. The reduction in the percentage of total seizures/28 days (drop and non-drop seizures) was also significantly reduced with cannabidiol 10
mg/kg/day (Study 2, 36% vs 18%) and cannabidiol 20 mg/kg/day (Study 1, 41% vs 14%; Study 2, 38% vs 18%). Cannabidiol was also associated with a greater improvement on the 7-point Subject/Caregiver Global Impression of Change scale. Patients had drop seizures (atonic, tonic, or tonic-clonic) inadequately controlled with 1 or more antiepileptic drugs (94% of patients used 2 or more antiepileptic drugs) with or without vagal nerve stimulation or ketogenic diet [1].

**Dravet Syndrome**

The effectiveness of Cannabidiol for the treatment of seizures associated with DS was demonstrated in a single randomized, double-blind, placebo-controlled trial in 120 patients aged 2 to 18 years. Study 3 compared a dose of Cannabidiol 20 mg/kg/day with placebo. Patients had a diagnosis of treatment-resistant DS and were inadequately controlled with at least one concomitant AED, with or without vagal nerve stimulation or ketogenic diet. During the 4-week baseline period, patients were required to have at least 4 convulsive seizures while on stable AED therapy. The baseline period was followed by a 2-week titration period and a 12-week maintenance period. The primary efficacy measure was the percent change from baseline in the frequency (per 28 days) of convulsive seizures (all countable atonic, tonic, clonic, and tonic-clonic seizures) over the 14-week treatment period. The median percentage change was -38.9% from baseline compared with 13.3% reduction with the addition of placebo.

In Study 3, 93% of patients were taking at least 2 concomitant AEDs during the trial. The most commonly used concomitant AEDs (>25%) in Study 3 were clobazam (65%), valproate (57%), stiripentol (43%), levetiracetam (28%), and topiramate (26%). The baseline median convulsive seizure frequency was 13 per 28 days for the combined groups.

The median percent change from baseline (reduction) in the frequency of convulsive seizures was significantly greater for Cannabidiol 20 mg/kg/day than for placebo. A reduction in convulsive seizures was observed within 4 weeks of initiating treatment with Cannabidiol and the effect remained generally consistent over the 14-week treatment period.

In Study 3, 4 of 60 (6.7%) patients treated with Cannabidiol 20 mg/kg/day reported no convulsive seizures during the maintenance period, compared to 0 patients in the placebo group.

Adverse events were more common with cannabidiol: treatment-related adverse events (75% vs 36%), serious adverse events (16% vs 5%), and elevated aminotransferase levels (20% vs 2%). Treatment-emergent adverse events included somnolence (36% vs 10%), diarrhea (31% vs 10%), decreased appetite (28% vs 5%), fatigue (20% vs 3%), pyrexia (15% vs 8%), vomiting (15% vs 5%), lethargy (13% vs 5%), and upper respiratory tract infections (11% vs 8%).[1,2,4].

**Special Considerations:**

Use within 12 weeks of first opening the bottle, then discard any remainder. According to the label, taking cannabidiol with a high-fat/high calorie can increase maximum serum concentrations of the drug 5-fold and the area under the
concentration/time curve (AUC) 4-fold. Advise patients of the potential for positive drug screens. [1,2].

**DEA Classification:**

Schedule V [1].

**Summary/Conclusion:**

Cannabidiol reduced the frequency of treatment-resistant convulsive seizures in patients with Dravet syndrome and drop seizures in those with Lennox-Gastaut syndrome, compared to placebo. These trials did not stratify patients for concomitant use of clobazam (cannabidiol increases serum concentrations of the active metabolite of clobazam 3-fold), which could have contributed to the positive results.

**Recommendation:**

Cannabidiol should be considered as a reserve drug in our formulary when treatment-resistant seizures are present and at least two AED’s have been trialed.

**References:**


*Prepared by:*

Bonnie Burroughs, Pharm.D., BCGP
Director of Pharmacy
Abilene State Supported Living Center
Texas HHSC Psychiatric Executive Formulary Committee

NEW DRUG APPLICATION FORM

For consideration of inclusion into the HHSC Psychiatric Drug Formulary

Date: 8-2-2019

Name of practitioner submitting the application: Catherine Hall

Name of entity with which the practitioner is associated by employment or contract (i.e., state hospital, state supported living center, state center, or local authority (state-operated community services (SOCS) or community MHMR center)):

San Antonio State Hospital

Requested by PEFC:

<table>
<thead>
<tr>
<th>Therapeutic Classification</th>
<th>Dipeptidyl peptidase-4 inhibitor, SGLT-2 inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic Name</td>
<td>Liraglutide</td>
</tr>
<tr>
<td>Trade Name(s)</td>
<td>Victoza</td>
</tr>
<tr>
<td>Manufacturer(s)</td>
<td>Novo Nordisk</td>
</tr>
<tr>
<td>Dosage Form(s)</td>
<td>SQ injection</td>
</tr>
</tbody>
</table>

**Information regarding new drug:**

- Explain the pharmacological action or use of this drug:
  - Dipeptidyl peptidase-4 inhibitor, SGLT-2 inhibitor
  - Slows gastric emptying, increases satiety
  - Helps with weight loss, improves CV outcomes

- Explain the advantages of this drug over those listed in the formulary:

- State which drugs this new drug would replace or supplement:
  - Metformin, Pioglitazone, Insulin, Alglucerase

- Application is approved [ ]
  - signature of chairman of facility pharmacy and therapeutics committee

- OR

- Application is appropriate and complete [ ]
  - signature of clinical/medical director or designee
**Liraglutide (Victoza®)**

**Classification:** Antidiabetic agent, Glucagon-Like Peptide-1 (GLP-1) receptor agonist

**Pharmacology:**

*Mechanism of Action*

Liraglutide (Victoza®) is an acylated human Glucagon-Like Peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1 (7-37). Like endogenous GLP-1 (7-37), liraglutide (Victoza®) activates GLP-1 receptors which are found in the hypothalamus, heart, gastrointestinal tract, and pancreas. Liraglutide (Victoza®)’s stimulation of GLP-1 receptors in the pancreatic beta cells leads to insulin release in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia. Liraglutide (Victoza®) also decreases glucagon secretion in a glucose-dependent manner, delays gastric emptying, and increases satiety.

Endogenous GLP-1 (7-37) has a half-life of 1.5-2 minutes because it is quickly degraded by endogenous dipeptidyl peptidase IV (DPP-IV) and other endopeptidases. Unlike endogenous GLP-1, liraglutide (Victoza®) is stable against metabolic degradation by endopeptidases and has a plasma half-life of 13 hours after subcutaneous administration.

*Pharmacodynamics*

Liraglutide (Victoza®) lowers fasting, premeal, and postprandial glucose throughout the day through glucose-dependent insulin secretion, lowered glucagon secretion (no impairment of glucagon response to low glucose concentrations) and delayed gastric emptying.

The effect of liraglutide (Victoza®) on cardiac repolarization was tested in a QTc study. Liraglutide (Victoza®) at steady state concentrations with daily doses up to 1.8 mg did not produce QTc prolongation.
**Indication:**

Liraglutide (Victoza®) is indicated as an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus. (approved January 2010)

Liraglutide (Victoza®) is indicated 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 mellitus and established cardiovascular disease.

**Limitations of Use**

Liraglutide (Victoza®) is not approved for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

Liraglutide (Victoza®) has not been studied in combination with prandial insulin.

**Pharmacokinetics**

**Table 1. LIRAGLUTIDE (VICTOZA®) pharmacokinetics**

<table>
<thead>
<tr>
<th>Absorption</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (peak) at 8-12 hrs (SQ), Bioavailability = 55% (SQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>V&lt;sub&gt;d&lt;/sub&gt; = 13 L, 0.07 L/kg (SQ, IV), extensively plasma protein bound (&gt;98%)</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Endogenously metabolized by dipeptidyl peptidase IV (DPP-IV) and endogenous endopeptidases. Metabolism occurs more slowly compared to endogenous GLP-1.</td>
</tr>
<tr>
<td>Excretion</td>
<td>Cl = 1.2 L/h (SQ), t&lt;sub&gt;1/2&lt;/sub&gt;=13 hrs (SQ), urine (6%, as metabolites), feces (5%, as metabolites)</td>
</tr>
</tbody>
</table>

**Elderly**

Age had no effect on the pharmacokinetics of liraglutide (Victoza®) based on a pharmacokinetic study in healthy elderly subjects (65 to 83 years) and population pharmacokinetic analyses of patients 18 to 80 years of age.

**Gender**

Based on the results of population pharmacokinetic analyses, females have 25% lower weight-adjusted clearance of liraglutide (Victoza®) compared to males. Based on the exposure response data, no dose adjustment is necessary based on gender.

**Race and Ethnicity**

Race and ethnicity had no effect on the pharmacokinetics of liraglutide (Victoza®) based on the results of population pharmacokinetic analyses that included Caucasian, Black, Asian and Hispanic/Non-Hispanic subjects.
**Body Weight**

Body weight significantly affects the pharmacokinetics of liraglutide (Victoza®) based on results of population pharmacokinetic analyses. The exposure of liraglutide (Victoza®) decreases with an increase in baseline body weight. However, the 1.2 mg and 1.8 mg daily doses of liraglutide (Victoza®) provided adequate systemic exposures over the body weight range of 40 – 160 kg evaluated in the clinical trials. **Liraglutide (Victoza®) was not studied in patients with body weight >160 kg.**

**Pediatric**

A population pharmacokinetic analysis was conducted for liraglutide (Victoza®) using data from 72 pediatric subjects (10 to 17 years of age) with type 2 diabetes. The pharmacokinetic profile of liraglutide (Victoza®) in the pediatric subjects was consistent with that in adults.

**Renal Impairment**

The single-dose pharmacokinetics of liraglutide (Victoza®) were evaluated in subjects with varying degrees of renal impairment. Subjects with mild (estimated creatinine clearance 50-80 mL/min) to severe (estimated creatinine clearance <30 mL/min) renal impairment and subjects with end-stage renal disease requiring dialysis were included in the trial. Compared to healthy subjects, liraglutide (Victoza®) AUC in mild, moderate, and severe renal impairment and in end-stage renal disease was on average 35%, 19%, 29% and 30% lower, respectively.

**Hepatic Impairment**

The single-dose pharmacokinetics of liraglutide (Victoza®) were evaluated in subjects with varying degrees of hepatic impairment. Subjects with mild (Child Pugh score 5-6) to severe (Child Pugh score > 9) hepatic impairment were included in the trial. Compared to healthy subjects, liraglutide (Victoza®) AUC in subjects with mild, moderate and severe hepatic impairment was on average 11%, 14% and 42% lower, respectively.

**Dosage/Administration**

Inspect visually prior to each injection. Only use if solution is clear, colorless, and contains no particles.

Inject liraglutide (Victoza®) subcutaneously once daily at any time of day, independently of meals in the abdomen, thigh, or upper arm. No dose adjustment is needed if changing the injection site and/or timing.

When using liraglutide (Victoza®) with insulin, administer as separate injections. Never mix.
It is acceptable to inject liraglutide (Victoza®) and insulin in the same body region, but the injections should not be adjacent to each other.

If a dose is missed, resume the once-daily regimen as prescribed with the next scheduled dose. Do not administer an extra dose or increase the dose to make up for the missed dose.

If more than 3 days has elapsed since the last liraglutide (Victoza®) dose, reinitiate liraglutide (Victoza®) at 0.6 mg to mitigate any gastrointestinal symptoms associated with restarting treatment.

**Adult Dosage**

Initiate liraglutide (Victoza®) at 0.6 mg daily for one week. The 0.6 mg is a starting dose intended to reduce gastrointestinal symptoms during initial titration and is not effective for glycemic control in adults. After one week at 0.6 mg per day, increase the dose to 1.2 mg daily. If additional glycemic control is required, increase the dose to 1.8 mg daily after one week of treatment with the 1.2 mg daily dose.

**Pediatric Dosage**

Initiate liraglutide (Victoza®) at 0.6 mg daily for at least one week. After at least one week at 0.6 mg daily, the dose may be increased to 1.2 mg daily if additional glycemic control is required. If additional glycemic control is required, increase the dose to 1.8 mg daily after at least one week of treatment with the 1.2 mg daily dose.

**Use in Special Population**

**Pregnancy**

Based on animal reproduction studies, there may be risks to the fetus from exposure to liraglutide (Victoza®) during pregnancy. Liraglutide (Victoza®) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Lactation**

There are no data on the presence of liraglutide (Victoza®) in human milk, the effects on the breastfed infant, or the effects on milk production. However, liraglutide (Victoza®) was found to be in present in breast milk in animal studies. Developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for liraglutide (Victoza®) and any potential adverse events on the breastfed infant from liraglutide (Victoza®) or from the underlying maternal condition.
Pediatric Use

The safety and effectiveness of liraglutide (Victoza®) as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus have been established in pediatric patients 10 years of age and older. The safety and effectiveness of liraglutide (Victoza®) has not been established in pediatric patients less than 10 years of age.

Geriatric Use

No overall treatment differences were observed between geriatric patients and younger patients in clinical trials, but greater sensitivity to liraglutide (Victoza®) for these older individuals cannot be ruled out.

Renal Impairment

No dose adjustment of liraglutide (Victoza®) is recommended for patients with renal impairment. The safety and efficacy of liraglutide (Victoza®) was evaluated in a 26-week clinical study that included patients with moderate renal impairment (eGFR 30 to 60 mL/min/1.73m²). In the liraglutide (Victoza®) treatment arm of the LEADER trial, 1932 (41.4%) patients had mild renal impairment, 999 (21.4%) patients had moderate renal impairment and 117 (2.5%) patients had severe renal impairment at baseline. No overall differences in safety or efficacy were seen in these patients compared to patients with normal renal function. There is limited experience with liraglutide (Victoza®) in patients with end stage renal disease with postmarketing reports of acute renal failure and worsening of chronic renal failure which may sometimes require hemodialysis. Use caution in patients who experience dehydration.

Hepatic Impairment

There is limited experience in patients with mild, moderate or severe hepatic impairment. Therefore, liraglutide (Victoza®) should be used with caution in this patient population. No dose adjustment of liraglutide (Victoza®) is recommended for patients with hepatic impairment.

Gastroparesis

Liraglutide (Victoza®) slows gastric emptying and has not been studied in patients with pre-existing gastroparesis.

Boxed Warning

Risk of Thyroid C-cell Tumors

Liraglutide (Victoza®) causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposure in both genders of rats and mice. It is unknown whether liraglutide (Victoza®) causes thyroid C-cell tumors,
including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide (Victoza®)-induced rodent thyroid C-cell tumors has not been determined.

Liraglutide (Victoza®) is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC with the use of liraglutide (Victoza®) 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 liraglutide (Victoza®).

**Contraindication**

Liraglutide (Victoza®) is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Liraglutide (Victoza®) is contraindicated in patients with a prior serious hypersensitivity reaction to liraglutide (Victoza®) or any of the product components. Serious hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with liraglutide (Victoza®).

**Precautions**

*Risk of Thyroid C-cell Tumors*

*(See Boxed Warning)*

Cases of MTC in patients treated with liraglutide (Victoza®) have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and liraglutide (Victoza®) use in humans.

*Pancreatitis*

Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been observed in patients treated with liraglutide (Victoza®). After initiation of liraglutide (Victoza®), observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiation to the back and which may or may not be accompanied by vomiting). Discontinue liraglutide (Victoza®) if pancreatitis is suspected, and do not restart if pancreatitis is confirmed.

In glycemic control trials of liraglutide (Victoza®), there have been 13 cases of pancreatitis among liraglutide (Victoza®)-treated patients and 1 case in a comparator (glimepiride) treated patient (2.7 vs. 0.5 cases per 1000 patient-
nine of the 13 cases with liraglutide (Victoza®) were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a liraglutide (Victoza®)-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse.

Liraglutide (Victoza®) has been studied in a limited number of patients with a history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on liraglutide (Victoza®).

Never Share a liraglutide (Victoza®) Pen Between Patients even if the needle is changed.

Use with Medications Known to Cause Hypoglycemia

Patients receiving liraglutide (Victoza®) in combination with an insulin secretagogue (e.g. sulfonylurea) or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin.

In pediatric patients 10 years of age and older, the risk of hypoglycemia was higher with liraglutide (Victoza®) regardless of concomitant antidiabetic therapies.

Renal Impairment

Liraglutide (Victoza®) has not been found to be directly nephrotoxic in animal studies or clinical trials. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in liraglutide (Victoza®)-treated patients. Some of these events were reported in patients without known underlying renal disease. Most of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Some of the reported events occurred in patients receiving one or more medications known to effect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including liraglutide (Victoza®). Use caution when initiating or escalating doses of liraglutide (Victoza®) in patients with renal impairment.

Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with liraglutide (Victoza®). If a hypersensitivity reaction occurs, discontinue liraglutide (Victoza®); treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity reaction to liraglutide (Victoza®).
Anaphylaxis and angioedema have been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to these reactions with liraglutide (Victoza®).

Acute Gallbladder Disease
In the LEADER trial, 3.1% of liraglutide (Victoza®)-treated patients versus 1.9% of placebo-treated patients reported an acute event of gallbladder disease, such as cholelithiasis or cholecystitis. Most events required hospitalization or cholecystectomy. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

Adverse Effects

Serious Adverse Reactions
Risk of Thyroid C-cell Tumors (See Precautions)
Pancreatitis (See Precautions)
Use with Medications Known to Cause Hypoglycemia (See Precautions)
Renal Impairment (See Precautions)
Hypersensitivity Reactions (See Precautions)

Common Adverse Reactions
The safety of liraglutide (Victoza®) in subjects with type 2 diabetes was evaluated in 5 glycemic control, placebo-controlled trials in adults and one trial of 52 weeks duration in pediatric patients 10 years of age and older. The data in Table 2 reflect exposure of 1673 adult patients to liraglutide (Victoza®) and a mean duration of exposure to liraglutide (Victoza®) of 37.3 weeks. The mean age of adult patients was 58 years, 4% were 75 years or older and 54% were male. The population was 79% White, 6% Black or African American, 13% Asian; 4% were of Hispanic or Latino ethnicity. At baseline the population had diabetes for an average of 9.1 years and a mean HbA1c of 8.4%. Baseline estimated renal function was normal or mildly impaired in 88.1% and moderately impaired in 11.9% of the pooled population. Table 2 shows common adverse reactions in adults, excluding hypoglycemia, associated with the use of liraglutide (Victoza®). These adverse reactions occurred more commonly on liraglutide (Victoza®) than on placebo and occurred in at least 5% of patients treated with liraglutide (Victoza®). Overall, the type, and severity of adverse reactions in adolescents and children aged 10 years and above were comparable to that observed in the adult population.

Table 2. Adverse reactions in ≥ 5% of LIRAGLUTIDE (VICTOZA®) (VICTOZA®)-treated patients
<table>
<thead>
<tr>
<th></th>
<th>Placebo n=661 (%)</th>
<th>Liraglutide (Victoza®) 1.2 mg n=645 (%)</th>
<th>Liraglutide (Victoza®) 1.8 mg n=1024 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NAUSEA</strong></td>
<td>5</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td><strong>DIARRHEA</strong></td>
<td>4</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td><strong>HEADACHE</strong></td>
<td>7</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td><strong>VOMITING</strong></td>
<td>2</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td><strong>DECREASED APPETITE</strong></td>
<td>1</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td><strong>DYSPEPSIA</strong></td>
<td>1</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>6</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td><strong>CONSTIPATION</strong></td>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Back Pain</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

**Other Adverse Reactions**

**Gastrointestinal Adverse Reactions**

In the pool of 5 glycemic control, placebo-controlled clinical trials, withdrawals due to gastrointestinal adverse reactions, occurred in 4.3% of liraglutide (Victoza®)-treated patients and 0.5% of placebo-treated patients. Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials.

**Injection Site Reactions**

Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of liraglutide (Victoza®)-treated patients in the five double-blind, glycemic control trials of at least 26 weeks duration. Less than 0.2% of liraglutide (Victoza®)-treated patients discontinued due to injection site reactions.

**Hypoglycemia**

In 5 adult glycemic control, placebo-controlled clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 8 liraglutide (Victoza®)-treated patients (7.5 events per 1000 patient-years). Of these 8 liraglutide (Victoza®)-treated patients, 7 patients were concomitantly using a sulfonylurea.

In a 26-week pediatric placebo-controlled clinical trial with a 26-week open-label extension, 21.2% of liraglutide (Victoza®) treated patients (mean age 14.6 years)
with type 2 diabetes, had hypoglycemia with a blood glucose <54 mg/dL with or without symptoms (335 events per 1000 patient years). No severe hypoglycemic episodes occurred in the liraglutide (Victoza®) treatment group (severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions).

**Papillary Thyroid Carcinoma**

In glycemic control trials of liraglutide (Victoza®), there were 7 reported cases of papillary thyroid carcinoma in patients treated with liraglutide (Victoza®) and 1 case in a comparator-treated patient (1.5 vs. 0.5 cases per 1000 patient-years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound.

**Cholelithiasis and Cholecystitis**

In glycemic control trials of liraglutide (Victoza®), the incidence of cholelithiasis was 0.3% in both liraglutide (Victoza®)-treated and placebo-treated patients. The incidence of cholecystitis was 0.2% in both liraglutide (Victoza®)-treated and placebo-treated patients.

In the LEADER trial, the incidence of cholelithiasis was 1.5% (3.9 cases per 1000 patient years of observation) in liraglutide (Victoza®)-treated and 1.1% (2.8 cases per 1000 patient years of observation) in placebo-treated patients, both on a background of standard of care. The incidence of acute cholecystitis was 1.1% (2.9 cases per 1000 patient years of observation) in liraglutide (Victoza®)-treated and 0.7% (1.9 cases per 1000 patient years of observation) in placebo-treated patients.

**Laboratory Tests**

**Bilirubin**

In the five glycemic control trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of liraglutide (Victoza®)-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown.

**Calcitonin**

Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. At the end of the glycemic control trials, adjusted mean serum calcitonin concentrations were higher in liraglutide (Victoza®)-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. Between group differences in adjusted mean serum calcitonin values were approximately 0.1 ng/L or less. Among patients with
pretreatment calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of liraglutide (Victoza®)-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients. The clinical significance of these findings is unknown.

Lipase and Amylase

In one glycemic control trial in renal impairment patients, a mean increase of 33% for lipase and 15% for amylase from baseline was observed for liraglutide (Victoza®)-treated patients while placebo-treated patients had a mean decrease in lipase of 3% and a mean increase in amylase of 1%.

In the LEADER trial, serum lipase and amylase were routinely measured. Among liraglutide (Victoza®)-treated patients, 7.9% had a lipase value at any time during treatment of greater than or equal to 3 times the upper limit of normal compared with 4.5% of placebo-treated patients, and 1% of liraglutide (Victoza®)-treated patients had an amylase value at any time during treatment of greater than or equal to 3 times the upper limit of normal versus 0.7% of placebo-treated patients.

The clinical significance of elevations in lipase or amylase with liraglutide (Victoza®) is unknown in the absence of other signs and symptoms of pancreatitis.

Vital signs

Liraglutide (Victoza®) did not have adverse effects on blood pressure. Mean increases from baseline in heart rate of 2 to 3 beats per minute have been observed with liraglutide (Victoza®) compared to placebo.

Immunogenicity

Patients treated with liraglutide (Victoza®) may develop anti-liraglutide antibodies. Approximately 50-70% of liraglutide (Victoza®)-treated patients in five double-blind clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these liraglutide (Victoza®)-treated patients. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the liraglutide (Victoza®)-treated patients in the double-blind 52-week monotherapy trial and in 4.8% of the liraglutide (Victoza®) treated patients in the double-blind 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on Liraglutide (Victoza®) in an in vitro assay occurred in 2.3% of the liraglutide (Victoza®)-treated patients in the double-blind 52-week monotherapy trial and in 1.0% of the liraglutide (Victoza®)-treated patients in the double-blind 26-week add-on combination therapy trials.
Antibody formation was not associated with reduced efficacy of liraglutide (Victoza®) when comparing mean HbA1c of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA1c with liraglutide (Victoza®) treatment.

In 5 double-blind glycemic control trials of liraglutide (Victoza®), events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of liraglutide (Victoza®)-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for liraglutide (Victoza®)-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies.

In the LEADER trial, anti-liraglutide antibodies were detected in 11 out of the 1247 (0.9%) liraglutide (Victoza®)-treated patients with antibody measurements. Of the 11 liraglutide (Victoza®)-treated patients who developed anti-liraglutide antibodies, none were observed to develop neutralizing antibodies to liraglutide, and 5 patients (0.4%) developed cross-reacting antibodies against native GLP-1.

In a clinical trial with pediatric patients 10 to 17 years, anti-liraglutide antibodies were detected in 1 (1.5%) liraglutide (Victoza®) treated patient at week 26 and 5 (8.5%) liraglutide (Victoza®) treated patients at week 53. None of the 5 had antibodies cross reactive to native GLP-1 or had neutralizing antibodies.

Post-Marketing Experience

Medullary thyroid carcinoma
Dehydration resulting from nausea, vomiting and diarrhea
Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis
Angioedema and anaphylactic reactions
Allergic reactions: rash and pruritus
Acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death
Hepatobiliary disorders: elevations of liver enzymes, hepatitis

Overdosage

Overdoses have been reported in clinical trials and post-marketing use of liraglutide (Victoza®). Effects have included severe nausea and severe vomiting. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient’s clinical signs and symptoms.

Monitoring

HbA1c (every 6 months in patients meeting treatment goals; every 3 months in patients not meeting therapy goals OR a change in therapy), blood glucose (as
indicated), renal function, hepatic function, signs/symptoms of acute gallbladder disease, signs/symptoms of pancreatitis

**Interactions**

*Oral Medications*

Liraglutide (Victoza®) delays gastric emptying and may impact absorption of concomitantly administered oral medications. In clinical pharmacology trials, liraglutide (Victoza®) did not affect the absorption of the tested orally administered medications to any clinically relevant degree. Nonetheless, caution should be exercised when oral medications are concomitantly administered with liraglutide (Victoza®).

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

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

**Efficacy**

In glycemic control trials, liraglutide (Victoza®) has been studied as monotherapy and in combination with one or two oral anti-diabetic medications or basal insulin. Liraglutide (Victoza®) was also studied in a cardiovascular outcomes trial (LEADER trial).

In each of the placebo-controlled trials, treatment with liraglutide (Victoza®) produced clinically and statistically significant improvements in hemoglobin A1c and fasting plasma glucose (FPG) compared to placebo.

All liraglutide (Victoza®)-treated patients started at 0.6 mg/day. The dose was increased in weekly intervals by 0.6 mg to reach 1.2 mg or 1.8 mg for patients randomized to these higher doses. Liraglutide (Victoza®) 0.6 mg is not effective for glycemic control and is intended only as a starting dose to reduce gastrointestinal intolerance.

*Monotherapy*

LEAD-3 Mono (NTC00294723) was a 52-week, randomized, phase III, double-blind, parallel-treatment trial that compares liraglutide (Victoza®) to glimepiride (AMARYL). The study was conducted in 746 adult patients 18-80 years of age with a body-mass index of 45 kg/m² or less, and a diagnosis of type 2 diabetes mellitus. These patients had previously been treated with diet and exercise OR up to half of the highest dose of oral antidiabetic drug monotherapy for at least 2 months. Patients were randomly assigned (1:1:1) to receive once daily subcutaneous Liraglutide (Victoza®) 1.2 mg or 1.8 mg or once daily oral glimepiride 8 mg.
Patients were excluded if they had been treated with insulin in the previous 3 months (except short-term treatment for intercurrent illness), treatment with systemic corticosteroids, hypoglycemia unawareness or recurrent severe hypoglycemia, and impaired liver function (aspartate aminotransferase or alanine aminotransferase concentrations ≥2.5 times upper normal range).

Baseline Characteristics

The mean age of participants was 53 years, and the mean duration of diabetes was 5 years. Mean baseline HbA1c and fasting plasma glucose values were 8.2% and 9.5 mmol/L (171 mg/dL), respectively. Mean baseline weight was 92.6 kg with a mean BMI of 33.1 kg/m². Mean blood pressure was 129/79 mm Hg.

Table 3: Baseline characteristics in the LEAD-3 Mono trial

<table>
<thead>
<tr>
<th>Randomized (ITT population)</th>
<th>Liraglutide (Victoza®) 1.2 mg</th>
<th>Liraglutide (Victoza®) 1.8 mg</th>
<th>Glimepiride 8 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>251</td>
<td>247</td>
<td>248</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.7 (11.0)</td>
<td>52.0 (10.8)</td>
<td>53.4 (10.9)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>33.2 (5.6)</td>
<td>32.8 (6.3)</td>
<td>33.2 (5.6)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>92.5 (19.2)</td>
<td>92.8 (20.7)</td>
<td>93.4 (19.2)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.3% (1.0%)</td>
<td>8.3% (1.1%)</td>
<td>8.4 (1.2%)</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)*</td>
<td>9.3 (2.6)</td>
<td>9.5 (2.6)</td>
<td>9.5 (2.6)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>127.6 (14.3)</td>
<td>128.1 (13.9)</td>
<td>130.0 (16.1)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78.5 (8.3)</td>
<td>78.8 (8.4)</td>
<td>79.5 (8.6)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or n (%) unless otherwise specified.
ITT=intention to treat.
*Fasting plasma glucose (mg/dL): Liraglutide (Victoza®) 1.2 mg = 167.4, Liraglutide (Victoza®) 1.8 mg = 171, Glimepiride 8 mg = 171

Results

The primary outcome was change in value of HbA1c from baseline to 52 weeks. Treatment with liraglutide (Victoza®) 1.8 mg and 1.2 mg resulted in a statistically significant reduction in HbA1c compared to glimepiride. HbA1c values decreased from baseline by 0.84% (SD 1.23) with liraglutide (Victoza®) 1.2 mg, 1.14% (1.24) with liraglutide (Victoza®) 1.8 mg, and 0.51% (1.20) with
glimepiride. Additionally, the reduction with liraglutide (Victoza®) 1.8 mg was significantly greater when compared to liraglutide (Victoza®) 1.2 mg (-0.29%; -0.50 to -0.09, p=0.0046). Overall, compared with 28% in the glimepiride group, 43% of participants treated with liraglutide (Victoza®) 1.2 mg (p=0.0007) and 51% on liraglutide (Victoza®) 1.8 mg (p<0.0001) reached the American Diabetes Association target HbA1c of less than 7.0%. The proportion of participants achieving these targets with liraglutide (Victoza®) 1.8 mg was significantly higher than with liraglutide (Victoza®) 1.2 mg.

Regarding secondary outcomes, decreases in fasting plasma glucose from baseline for the liraglutide (Victoza®) groups were significantly greater than those in the glimepiride group with values of 8.65 mmol/L (SD 3.17) [155.7 mg/dL], 8.25 mmol/L (SD 2.75) [148.5 mg/dL], and 9.27 mmol/L (SD 2.99) [166.9 mg/dL] in the liraglutide (Victoza®) 1.2 mg, liraglutide (Victoza®) 1.8 mg, and glimepiride groups, respectively. A greater proportion of participants in the Liraglutide (Victoza®) groups achieved the American Diabetes Association fasting plasma glucose target (5.0–7.2 mmol/L) [90-130 mg/dL] than in the glimepiride group (37.6% and 41.4% vs 22.2% for the liraglutide (Victoza®) 1.2 mg and 1.8 mg vs glimepiride group, respectively, p≤0.0001 for each comparison). Additionally, participants in the liraglutide (Victoza®) groups lost weight whereas those taking glimepiride gained weight. To determine if persistent nausea was a factor in weight loss, participants were analyzed by the number of days they had nausea (>7 days or ≤7 days). Participants who had nausea for more than 7 days (29 on liraglutide (Victoza®) 1.2 mg, 38 on liraglutide (Victoza®) 1.8 mg, and nine on glimepiride) had a mean weight change of –3.24 kg, –3.39 kg, and –1.43 kg, compared with –1.85 kg, –2.26 kg, and +1.22 kg, respectively, for those with no nausea or up to 7 days of nausea (the differences were not statistically significant for any treatment). Also, regarding blood pressure changes, systolic blood pressure fell by 0.7 mmHg (SD 13.7) in the glimepiride group compared with 2.1 mmHg (SD 14.2) in the liraglutide (Victoza®) 1.2 mg group (p=0.2912) and 3.6 mmHg (14.1) in the liraglutide (Victoza®) 1.8 mg group (p<0.0118). Mean diastolic blood pressure fell slightly but not significantly for all treatment groups.

Safety

Key safety assessments were tolerability (including nausea and other gastrointestinal adverse events), serum calcitonin (tumor marker for neoplasia of thyroid C-cells), and hypoglycemic episodes (defined as measured plasma glucose <3.1 mmol/L or <55.8 mg/dL). **No major hypoglycemia events (requiring third-party assistance) occurred.** However, 12% and 8% of participants in the liraglutide (Victoza®) 1.2 mg and 1.8 mg groups, respectively, had minor hypoglycemia (plasma glucose <3.1 mmol/L or <55.8 mg/dL), compared with 24% in the glimepiride group. The rate of minor hypoglycemia was significantly lower (p<0.0001) for both liraglutide (Victoza®) treatment groups (0.30 and 0.25 events
per year for liraglutide (Victoza®) 1.2 mg and 1.8 mg, respectively, compared with 1.96 events per year for glimepiride). The most common side effects with liraglutide (Victoza®) use included nausea, vomiting, and diarrhea. 27.5% and 29.3% of participants in the liraglutide (Victoza®) 1.2 mg and 1.8 mg groups, respectively, reported nausea, compared with 8.5% in the glimepiride group (p<0.0001 for both comparisons). 9.3%, 12.4%, and 3.6% of participants in the liraglutide (Victoza®) 1.2 mg and 1.8 mg, and glimepiride groups, respectively, reported vomiting (p<0.0001 for both comparisons with glimepiride). 8.9% in the glimepiride group reported diarrhea compared with 15.5% and in the liraglutide (Victoza®) 1.2 mg group (p=0.0283) and 18.7% in the liraglutide (Victoza®) 1.8 mg group (p=0.0017). 11 (4%) of 251 and 6 (2%) of 246 participants taking liraglutide (Victoza®) 1.2 mg and 1.8 mg, respectively, withdrew from the study because of vomiting, nausea, or diarrhea, compared with none of 248 in the glimepiride group. Mean pulse rate increased by 3.2, 1.6, and 0.4 beats per min for liraglutide (Victoza®) 1.2 mg and 1.8 mg, and glimepiride group, respectively (p=0.0027 and p=0.1422 for liraglutide (Victoza®) 1.2 mg and 1.8 mg, respectively, vs glimepiride). After 52 weeks, calcitonin concentrations did not differ in participants taking liraglutide (Victoza®) and those taking glimepiride. Two participants had pancreatitis, one after 197 liraglutide (Victoza®) 1.2 mg days of treatment and another after 333 liraglutide (Victoza®) 1.8 mg days of treatment. Both patients recovered; one continued in the study (1.2 mg).

Add-on to Metformin

The LEAD-2 trial (NCT00318461) was a 26-week, double-blind, double-dummy, placebo- and active-controlled, parallel-group trial comparing liraglutide (Victoza®) to glimepiride (AMARYL) or placebo as an addition to metformin. This study was conducted in 1091 adult patients with type 2 diabetes between 18–80 years of age with a ≤BMI 40 kg/m2. HbA1C levels were between 7 and 11% (pre-study oral antidiabetes (OAD) monotherapy for ≥3 months) or between 7 and 10% (pre-study combination OAD therapy for ≥3 months). Subjects were excluded if they had used insulin during the previous 3 months (except short-term treatment).

Subjects were randomly assigned (2:2:2:1:2) to receive one of three once-daily doses of liraglutide (Victoza®) (0.6, 1.2, or 1.8 mg/day) injected subcutaneously in combination with metformin, to receive liraglutide (Victoza®) placebo with metformin monotherapy (placebo group), or to receive combination therapy with glimepiride and metformin (4 mg glimepiride once daily with the first meal of the day). Metformin could be decreased to a minimum of 1,500 mg/day in the case of unacceptable hypoglycemia or other adverse events but had to be maintained between 1,500 and 2000 mg/day during the maintenance period.
Baseline Characteristics

Baseline Characteristics of the study population were balanced across treatment groups (Table 4) with a mean age of 57 years, and a mean duration of diabetes was 7 years. The mean BMI was 31.0 kg/m². The majority (65%) of the randomly assigned subjects were treated with two OADs before the study.

Table 4. Baseline characteristics in the LEAD-2 trial

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide (Victoza®) 0.6 mg</th>
<th>Liraglutide (Victoza®) 1.2 mg</th>
<th>Liraglutide (Victoza®) 1.8 mg</th>
<th>Glimepiride 4 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized (ITT and safety population)</td>
<td>242</td>
<td>240</td>
<td>242</td>
<td>242</td>
<td>121</td>
</tr>
<tr>
<td>Sex: male/female (%)</td>
<td>62/38</td>
<td>54/46</td>
<td>59/41</td>
<td>57/43</td>
<td>60/40</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 (11)</td>
<td>57 (9)</td>
<td>57 (9)</td>
<td>57 (9)</td>
<td>56 (9)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>7 (5)</td>
<td>7 (5)</td>
<td>8 (5)</td>
<td>8 (5)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Prestudy OAD Treatment</td>
<td>81 (34)</td>
<td>91 (38)</td>
<td>83 (34)</td>
<td>89 (37)</td>
<td>41 (34)</td>
</tr>
<tr>
<td>(monotherapy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prestudy OAD Treatment</td>
<td>161 (67)</td>
<td>150 (62)</td>
<td>159 (66)</td>
<td>155 (63)</td>
<td>81 (66)</td>
</tr>
<tr>
<td>(combination therapy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m³)</td>
<td>30.5 (4.8)</td>
<td>31.1 (4.8)</td>
<td>30.9 (4.6)</td>
<td>31.2 (4.6)</td>
<td>31.6 (4.4)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.4 (0.9)</td>
<td>8.3 (1.0)</td>
<td>8.4 (1.0)</td>
<td>8.4 (1.0)</td>
<td>8.1 (1.1)</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)*</td>
<td>10.2 (2.4)</td>
<td>9.9 (2.3)</td>
<td>10.1 (2.3)</td>
<td>10.0 (2.6)</td>
<td>10.0 (2.3)</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>131 (14)</td>
<td>132 (14)</td>
<td>131 (14)</td>
<td>132 (16)</td>
<td>135 (16)</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>80 (8)</td>
<td>80 (10)</td>
<td>79 (8)</td>
<td>80 (8)</td>
<td>81 (9)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or n (%) unless otherwise noted.

ITT = intention to treat

*Fasting plasma glucose (mg/dL): Liraglutide (Victoza®) 0.6 mg = 183.6, Liraglutide (Victoza®) 1.2 mg = 178.2, Liraglutide (Victoza®) 1.8 mg = 181.8, Glimepiride 4 mg = 180, Placebo = 180
Results

The primary outcome was change in HbA1c at the end of the study. At the end of the study, the mean HbA1c values for the overall population decreased by 0.7% (0.1) for the liraglutide (Victoza®) 0.6 mg group and by 1.0% (0.1) in the liraglutide (Victoza®) 1.2 and 1.8 mg group as well as in the glimepiride group. The HbA1c increased by 0.1% (0.1) for the placebo group. Liraglutide (Victoza®) was found to be more efficacious compared to placebo in reducing HbA1c but noninferior to glimepiride. The change from baseline HbA1c decreases were found to be slightly greater in the monotherapy group than in the combination therapy.

Regarding secondary outcomes, the decrease of fasting plasma glucose from baseline for all of the liraglutide (Victoza®) groups (-1.1, -1.6, and -1.7 mmol/l for 0.6, 1.2, and 1.8 mg liraglutide (Victoza®) groups, respectively) [-19.8, -28.8, -30.6 mg/dL] was significantly greater than the increase observed for the placebo group (0.4 mmol/l, P <0.0001) [7.2 mg/dL] but was similar to the decrease observed for the glimepiride group (-1.3 mmol/l) [-23.4 mg/dL]. Additionally, weight loss was dose dependent in the liraglutide (Victoza®) treatment groups [1.8 (0.2), 2.6 (0.2), and 2.8 (0.2) kg for 0.6, 1.2, and 1.8 mg Liraglutide (Victoza®) groups, respectively] and was significantly different (P<0.0001) from the weight gain in the glimepiride group [1.0 (0.2) kg]. The weight losses in the 1.2 and 1.8 mg Liraglutide (Victoza®) groups were also significantly greater (P≤0.01) than the weight loss in the placebo group [1.5 (0.3) kg]. Also, the 1.2 and 1.8 mg liraglutide (Victoza®) groups had significant reductions in systolic blood pressure (SBP) of 2–3 mmHg compared with the increase in SBP of 0.4 mmHg observed in the glimepiride group (treatment difference compared with glimepiride: 1.2 mg liraglutide (Victoza®), -3.2 mmHg, P=0.0128; 1.8 mg liraglutide (Victoza®), -2.7 mmHg, P = 0.0467). The decreases in SBP in the 0.6 mg liraglutide (Victoza®) and placebo groups were 0.6 and 1.8 mmHg, respectively.

Safety

Gastrointestinal disorders (nausea, vomiting, and diarrhea) were the most frequently reported adverse events in the liraglutide (Victoza®) groups and were reported during the study by 35, 40, and 44% of the subjects in the 0.6, 1.2, and 1.8 mg liraglutide (Victoza®) groups, respectively, and by 17% in the placebo and glimepiride groups. Overall, nausea alone was experienced by 11, 16, and 19% of the subjects in the 0.6, 1.2, and 1.8 mg liraglutide (Victoza®) groups, respectively; however, <10% of the subjects were experiencing nausea on a weekly basis by week 4. Vomiting was experienced by 5–7% in the liraglutide (Victoza®) groups and by 1% in the placebo and glimepiride groups; diarrhea was experienced by 10, 8, and 15% in the 0.6, 1.2, and 1.8 mg liraglutide (Victoza®) groups, respectively, and by 4% in the placebo and glimepiride groups. The percentages of subjects withdrawn because of adverse events were generally greater in the liraglutide (Victoza®) groups than in the glimepiride or placebo groups. Nausea, vomiting,
and/or diarrhea were the gastrointestinal events that led to the withdrawal of 36 liraglutide (Victoza®)-treated subjects (5% of all liraglutide (Victoza®)-treated subjects) in a dose-dependent manner. One subject in the 1.2 mg liraglutide (Victoza®) group and one in the glimepiride group were withdrawn for acute pancreatitis during the study. Neither subject had a prior history of pancreatitis, and both subjects were hospitalized for 7 days and subsequently recovered. In general, minor hypoglycemia occurred at low incidence (3% of subjects in the placebo and liraglutide (Victoza®) groups and 17% in the glimepiride group), resulting in a relatively low rate of reported minor hypoglycemia (0.03–0.14 events/year for the placebo and liraglutide (Victoza®) groups and 1.23 events/year for the glimepiride group) that was significantly less for all three liraglutide (Victoza®) groups than for the glimepiride group (P<0.001). No major hypoglycemia events were reported. No significant differences in calcitonin laboratory values were found between the liraglutide (Victoza®) groups and either the placebo or glimepiride group. Slight increases in pulse rate were observed in all treatment groups (2–3 bpm in the liraglutide (Victoza®) groups and 1 bpm in the glimepiride and placebo groups). The increases in pulse in the 0.6 and 1.2 mg liraglutide (Victoza®) groups were significantly greater than that in the glimepiride group (P = 0.012 and P = 0.024, respectively).

LIRAGLUTIDE (VICTOZA®) Compared to Sitagliptin, Both as Add-on to Metformin

In a 26–week, randomized, parallel-group, open-label trial (NCT00700817), liraglutide (Victoza®) was compared to sitagliptin (JANUVIA) as an add-on to metformin for patients with type 2 diabetes who did not achieve adequate glycemic control with metformin monotherapy.

Patients were included in this study if they were aged 18–80 years, had type 2 diabetes mellitus, had a HbA1c of 7.5–10.0%, a BMI of 45.0 kg/m² or lower, and had been treated with metformin (≥1500 mg daily) for 3 months or longer.

The main exclusion criteria were: previous treatment with any antihyperglycemic drug apart from metformin within 3 months of the trial; recurrent major hypoglycemia or hypoglycemic unawareness; present use of any drug except metformin that could affect glucose; contraindication to trial drugs; impaired renal or hepatic function; clinically significant cardiovascular disease; or cancer.

Participants were randomly assigned in a 1:1:1 ratio to receive 1.2 mg or 1.8 mg subcutaneous liraglutide (Victoza®) once daily, or 100 mg oral sitagliptin once daily.

Baseline Characteristics

The mean age of participants was 56 years, and the mean HbA1c was 8.5% (SD 0.7) at baseline with an average duration of diabetes of 6 years. The mean BMI was 32.8 kg/m².
Table 5. Baseline Characteristics in the LIRAGLUTIDE (VICTOZA®) (VICTOZA®) vs JANUVIA trial

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide (Victoza®) 1.2 mg</th>
<th>Liraglutide (Victoza®) 1.8 mg</th>
<th>Sitagliptin 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized (ITT population)</td>
<td>225</td>
<td>221</td>
<td>219</td>
</tr>
<tr>
<td>Men</td>
<td>116 (52%)</td>
<td>116 (52%)</td>
<td>120 (55%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.9 (9.6)</td>
<td>55.0 (9.1)</td>
<td>55.0 (9.0)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>6.0 (4.5)</td>
<td>6.4 (5.4)</td>
<td>6.3 (5.4)</td>
</tr>
<tr>
<td>Body mass index (kg/m³)</td>
<td>32.6 (5.2)</td>
<td>33.1 (5.1)</td>
<td>32.6 (5.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>93.7 (18.4)</td>
<td>94.6 (18.1)</td>
<td>93.1 (18.9)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.4% (0.8%)</td>
<td>8.4% (0.7%)</td>
<td>8.5 (0.7%)</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)*</td>
<td>10.1 (2.4)</td>
<td>9.9 (2.4)</td>
<td>10.0 (2.0)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>131.2 (14.4)</td>
<td>133.4 (14.5)</td>
<td>132.1 (14.8)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80.3 (9.0)</td>
<td>81.5 (8.5)</td>
<td>81.9 (9.1)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or n (%) unless otherwise noted.

ITT = intention to treat

*Fasting plasma glucose (mg/dL): Liraglutide (Victoza®) 1.2 mg = 181.8, Liraglutide (Victoza®) 1.8 mg = 178.2, Sitagliptin 100 mg = 180

The primary efficacy endpoint was change in HbA1c from baseline to week 26. In the superiority comparison, HbA1c reductions were superior with 1.2 mg and 1.8 mg liraglutide (Victoza®) versus sitagliptin. Mean decreases in HbA1c from baseline were −1.50% (95% CI −1.63 to −1.37) for 1.8 mg liraglutide (Victoza®), −1.24% (−1.37 to −1.11) for 1.2 mg liraglutide (Victoza®), and −0.90% (−1.03 to −0.77) for sitagliptin.

Regarding secondary outcomes, significantly more participants achieved the HbA1c targets (<7.0% and ≤6.5%) with liraglutide (Victoza®) than with sitagliptin: for HbA1c of less than 7.0%, ORs versus sitagliptin were 4.50 (95% CI 2.90–6.97) for 1.8 mg liraglutide (Victoza®), and 2.75 (1.78–4.25) for 1.2 mg liraglutide (Victoza®); and for HbA1c of 6.5% or lower, ORs versus sitagliptin were 4.25 (2.55–7.08) for 1.8 mg liraglutide (Victoza®), and 2.11 (1.24–3.59) for 1.2 mg liraglutide (Victoza®). After 26 weeks, mean decreases in fasting plasma glucose were significantly greater with liraglutide (Victoza®) than with sitagliptin: −2.14 mmol/L (95% CI −2.43 to −1.84) [−38.5 mg/dL] for 1.8 mg Liraglutide (Victoza®); −1.87 mmol/L (−2.16 to −1.57) [−33.7 mg/dL] for 1.2 mg Liraglutide (Victoza®), and −0.83 mmol/L (−1.13 to −0.54) [−14.9 mg/dL] for sitagliptin. Mean weight loss
after 26 weeks was significantly greater with Liraglutide (Victoza®) than with sitagliptin: −3.38 kg (95% CI −3.91 to −2.84) for 1.8 mg Liraglutide (Victoza®); −2.86 kg (−3.39 to −2.32) for 1.2 mg Liraglutide (Victoza®), and −0.96 kg (−1.50 to −0.42) for sitagliptin. Both liraglutide (Victoza®) and sitagliptin had a small effect on systolic and diastolic blood pressure; lowering of diastolic blood pressure with sitagliptin seemed to be significant versus 1.8 mg Liraglutide (Victoza®), but not versus 1.2 mg Liraglutide (Victoza®). Heart rate increased with liraglutide (Victoza®) and decreased slightly with sitagliptin; differences were small but significant for both doses of liraglutide (Victoza®) versus sitagliptin. Changes in the lipid profile between liraglutide (Victoza®) and sitagliptin were not significant, apart from the decrease in total cholesterol which was significantly greater with 1.8 mg liraglutide (Victoza®) than with sitagliptin.

Safety

More treatment-emergent adverse events were reported with liraglutide (Victoza®) than with sitagliptin. The most common adverse events were gastrointestinal symptoms, especially with liraglutide (Victoza®), and infections and infestations, which occurred with similar frequency in all treatment groups. Nausea occurred in a higher proportion of patients on Liraglutide (Victoza®) than on sitagliptin but was transient with in patients with nausea with a median duration of 13 days (IQR 5–28) with 1.2 mg liraglutide (Victoza®), 8 days (IQR 3–30) with 1.8 mg liraglutide (Victoza®). One patient on 1.2 mg liraglutide (Victoza®) had a major hypoglycemic episode (blood glucose concentration of 3.6 mmol/L or 64.8 mg/dL); no seizures or coma occurred. Minor hypoglycemia was reported by similar proportions of participants treated with 1.8 mg liraglutide (Victoza®) (11 [5%], 0.370 episodes per participant-year), 1.2 mg liraglutide (Victoza®) (12 [5%], 0.178), and sitagliptin (10 [5%], 0.106). There was one thyroid disorder reported in a patient on liraglutide (Victoza®), but histology showed no signs of a malignancy. Change from baseline in serum calcitonin concentrations, monitored for any effect on C-cell function, was similar across groups. No pancreatitis occurred in this study.

Combination Therapy with Metformin and Insulin

This trial (NCT00856986) was a 38 week, open-label trial evaluating the efficacy of the addition of liraglutide (Victoza®) to metformin in type 2 diabetes. If participants continued to have a HbA1C ≥7% while concomitantly on metformin and liraglutide (Victoza®) therapy, initiation of basal insulin (detemir) occurred.

Participants were included in the study if they were insulin-naïve (18-80 years) with type 2 diabetes treated for ≥3 months with either (1) ≥1,500 mg/day metformin (A1C values of 7.9-10.0%) or (2) ≥1,500 mg/day metformin and sulfonylurea (A1C values of 7.9-8.5%). The sulfonylurea doses utilized were less than original to half of the maximum approved dose.
This trial conducted in 988 participants was comprised of a 12-week run-in followed by a 26-week randomized period for participants not achieving <7% A1C at the end of the 12-week run-in. At run-in start, sulfonylureas were discontinued (in approximately one-third of participants), and liraglutide (Victoza®) was initiated. The metformin dose remained unchanged. Participants with an A1C ≥7% at the end of run-in were randomized (1:1) to 26 weeks of insulin detemir added to metformin + liraglutide (Victoza®) 1.8 mg (randomized treatment group) or continued metformin + liraglutide (Victoza®) 1.8 mg only (randomized control group). To determine the effects of continued treatment on initial responders, participants with A1C <7% after run-in were followed for 26 weeks as a prespecified observational group.

Table 6. LIRAGLUTIDE (VICTOZA®) with metformin and insulin trial design

<table>
<thead>
<tr>
<th>Screening</th>
<th>Run-in Period (12 weeks)</th>
<th>Randomized Period (26 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>metformin +/- sulfonylurea</td>
<td>metformin + liraglutide (Victoza®) 1.8 mg</td>
<td>OBSERVATIONAL GROUP (A1C&lt;7%)* metformin + liraglutide (Victoza®) 1.8 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RANDOMIZED TREATMENT GROUP (A1C≥7%)* metformin + liraglutide (Victoza®) 1.8 mg + insulin detemir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RANDOMIZED CONTROL GROUP (A1C≥7%)* metformin + Liraglutide (Victoza®) 1.8 mg</td>
</tr>
</tbody>
</table>

*The A1C values are based on the values at the end of the run-in period.

Baseline Characteristics

The mean age of participants was 57 years, and the mean duration of diabetes was 8 years. The mean BMI was 34.0 kg/m².

Table 7. LIRAGLUTIDE (VICTOZA®) with metformin and insulin baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Randomized treatment group (metformin + liraglutide (Victoza®) 1.8 mg + insulin detemir)</th>
<th>Randomized control group (metformin + liraglutide (Victoza®) 1.8 mg)</th>
<th>Observational group (metformin + liraglutide (Victoza®) 1.8 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>162</td>
<td>161</td>
<td>498</td>
</tr>
</tbody>
</table>

At the start of the run-in period

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Duration of diabetes (years)</th>
<th>Male: female (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>56.8 (9.4)</td>
<td>8.6 (5.8)</td>
<td>54.3:45.7</td>
</tr>
<tr>
<td></td>
<td>57.3 (9.8)</td>
<td>8.5 (6.0)</td>
<td>55.3:44.7</td>
</tr>
<tr>
<td></td>
<td>56.5 (9.7)</td>
<td>6.6 (5.7)</td>
<td>56.6:43.4</td>
</tr>
</tbody>
</table>
### AT THE START OF RANDOMIZATION PERIOD

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>96.0 (20.9)</th>
<th>95.3 (21.1)</th>
<th>94.7 (20.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C (%)</td>
<td>7.6 (0.6)</td>
<td>7.6 (0.7)</td>
<td>6.4 (0.4)</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)**</td>
<td>9.2 (1.9)</td>
<td>8.8 (2.1)</td>
<td>7.2 (1.3)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>132.2 (16.8)</td>
<td>131.7 (14.9)</td>
<td>128.9 (15.2)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79.6 (9.8)</td>
<td>80.9 (9.4)</td>
<td>79.4 (9.5)</td>
</tr>
</tbody>
</table>

Data are reported in mean (SD) or n (%) unless otherwise specified.

*Fasting plasma glucose (mg/dL): randomized treatment group = 183.6, randomized control group = 185.4, observational group = 165.6

**Fasting plasma glucose (mg/dL): randomized treatment group = 165.6, randomized control group = 158.4, observational group = 129.6

**Efficacy**

821 participants completed the run-in period, and 498 (61%) reached <7% A1C; 323 (39%) did not and were eligible for randomization. At run-in completion, A1C was reduced by 1.3% in this observational group and by 0.6% in the randomized groups from A1C values at run-in start of 7.7 and 8.3%, respectively; weight decreased by 3.5–4.4 kg and FPG by 1.0–2.0 mmol/L (18 – 36 mg/dL). Participants not reaching glycemic target had a 7.6% mean A1C at completion of the run-in period.

The primary end point was A1C change between randomized groups during the randomized period. Addition of insulin detemir further reduced A1C compared with continued metformin + liraglutide (Victoza®) (-0.51% [n = 162] vs. + 0.02% [n = 157], respectively; estimated treatment difference [ETD] -0.52 [95% CI -0.68 to -0.36]; P<0.0001), resulting in A1C values of 7.1 and 7.5%, respectively, at week 26, and meeting the trial’s primary end point. Additionally, mean FPG decreased more in the detemir (-2.1 mmol/L or -37.8 mg/dL) than
control group (-0.4 mmol/L; ETD -1.7 [-2.2 to -1.3]; P<0.0001) [-7.2 mg/dL]. After a mean 3.5-kg weight loss during the run-in period, both randomized groups experienced further modest weight reduction over the next 26 weeks during the randomized period: -0.16 kg with detemir and -0.95 kg without (ETD 0.79[0.08–1.49]; P = 0.03). There were no significant differences between the randomized groups in changes from randomization for serum lipids, except for free fatty acids (insulin detemir group, 20.11 mmol/L; control group, 20.03 mmol/L; ETD 20.08 [95% CI 20.13 to 20.03];P = 0.002). At 26 weeks, systolic blood pressure was reduced from run-in start by 3.13 mmHg in the control group, 1.65 mmHg in the insulin detemir group, and 3.33 mmHg in the observational group. Heart rate was increased from run-in start to 26 weeks in all treatment groups including the observational group: by 3.62 beats per minute (bpm) in the control group, 3.87 bpm in the insulin detemir group, and 3.64 bpm in the observational group.

The 498 participants in the observational group experienced a mean 1.3% A1C reduction by the end of run-in, and 1.1% reduction overall from start of run-in to week 26 (from 7.7% at run-in start to 6.6% at study end). The group also experienced overall reductions from start of run-in to week 26 in FPG of 2.1 mmol/L [37.8 mg/dL] (from 9.2 mmol/L or 165.6 mg/dL at run-in start to 7.2 mmol/L or 129.6 mg/dL) and weight reduction of 4.8 kg (from 99.0 kg at run-in start to 94.6 kg).

Safety

During the run-in, 167 of 988 (17%) participants withdrew; 76 of 167 (46%) of these withdrew due to gastrointestinal AEs (7.7% of enrolled participants). One major hypoglycemic event occurred (blood glucose level, 5.2 mmol/L or 93.6 mg/dL) and minor hypoglycemia occurred at 0.000–0.372 events per participant-year. Nausea was the most frequently reported run-in adverse event but incidences fell to <7% in all groups after 3 weeks. One case of acute pancreatitis was reported. In another participant, with elevated calcitonin level (23.5 ng/L) before liraglutide (Victoza®) administration, a subsequent thyroidectomy revealed an incidental thyroid neoplasm (1-mm papillary microcarcinoma).

In the randomization period, a total of 67% (109 of 163) and 59% (93 of 159) of participants had one or more adverse events, and 5.5% (9 participants; 13 events) and 3.8% (6 participants; 8 events) had serious adverse events, in the insulin detemir and control groups, respectively. Additionally, although more adverse events of increased lipase were reported with insulin detemir, a minor increase in the median serum lipase levels (below the upper limit of normal) was observed across all groups, without apparent treatment differences. One case of chronic pancreatitis occurred in the control group.
In the observational group over the entire 38-week period, 81% (402 of 499) of participants had adverse events and 7.8% (39 of 499) experienced 49 serious adverse events, with 45 considered unlikely to be related to study drug and without obvious pattern. No major hypoglycemic episodes occurred, whereas 9.0% (45 of 499) of participants experienced minor hypoglycemia (0.211 events per participant-year).

**Glycemic Control Trial in Pediatric Patients 10 Years of Age and Older with Type 2 Diabetes Mellitus**

This study (NCT01541215) was a 26-week, double-blind, randomized, parallel group, placebo controlled multi-center trial followed by a 26-week open-label extension period that looked at the efficacy and safety of liraglutide (Victoza®) as an adjuvant to metformin for glycemic control in youth with type 2 diabetes.

The study was conducted in 134 pediatric patients with type 2 diabetes aged 10-17 years old, with glycated hemoglobin levels between 7.0-11.0% if they were being treated with diet and exercise alone or between 6.5 and 11.0% if they were being treated with metformin (with or without insulin), and had a body-mass index (BMI) greater than the 85th percentile (with an age- and sex-matched population as reference).

Patients were excluded if they had type 1 diabetes, maturity-onset diabetes of the young, a fasting C-peptide level of less than 0.6 ng per milliliter, or antibodies against insulinoma-associated 2 or glutamic acid decarboxylase. Other exclusion criteria were the use of any antidiabetic agent other than metformin or basal insulin within 90 days before screening; a history of pancreatitis; serum calcitonin levels of 50 ng or more per liter; a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2; an alanine aminotransferase level 2.5 times the upper limit of the normal range or higher; serum creatinine levels greater than the upper limit of the normal range for age; a recent history of heart disease, proliferative retinopathy or maculopathy; recurrent severe hypoglycemia or hypoglycemic unawareness; and use of any drug (except metformin and/or basal insulin) which, in the investigator’s opinion, could interfere with the blood glucose level (e.g. systemic corticosteroids).

Patients were randomized to liraglutide (Victoza®) once-daily or placebo once-daily in combination with metformin with or without basal insulin treatment. All patients were on a metformin dose of 1000 to 2000 mg prior to randomization. The basal insulin dose was decreased by 20% at randomization and liraglutide (Victoza®) was titrated weekly by 0.6 mg for 2 to 3 weeks based on tolerability and an average fasting plasma glucose goal of <110 mg/dL.
Baseline Characteristics

The mean age was 14.6 years: 29.9% were ages 10-14 years, and 70.1% were greater than 14 years of age. 38.1% were male. The mean BMI was 33.9 kg/m². 18.7% of patients were using basal insulin at baseline. The mean duration of diabetes was 1.9 years and the mean HbA1c was 7.8%.

Table 8. Baseline Characteristics in LIRAGLUTIDE (VICTOZA®) in pediatrics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Liraglutide (Victoza®)</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized (ITT population)</td>
<td>66</td>
<td>68</td>
<td>134</td>
</tr>
<tr>
<td>Female</td>
<td>62.1%</td>
<td>61.8%</td>
<td>61.9%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>14.6 (1.7)</td>
<td>14.6 (1.7)</td>
<td>14.6 (1.7)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>1.9 (1.7)</td>
<td>1.9 (1.3)</td>
<td>1.9 (1.5)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>34.55 (10.87)</td>
<td>33.27 (7.36)</td>
<td>33.90 (9.25)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>93.3 (31.0)</td>
<td>89.8 (22.1)</td>
<td>91.5 (26.8)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.87 (1.35)</td>
<td>7.69 (1.34)</td>
<td>7.78 (1.34)</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>156.8 (52.2)</td>
<td>146.8 (38.3)</td>
<td>151.7 (45.8)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>118.4 (11.4)</td>
<td>115.3 (12.0)</td>
<td>116.8 (11.8)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>73.2 (8.5)</td>
<td>71.2 (7.6)</td>
<td>72.2 (8.1)</td>
</tr>
<tr>
<td>Metformin dose at baseline - mg</td>
<td>1912 (286)</td>
<td>1877 (384)</td>
<td>1894 (339)</td>
</tr>
<tr>
<td>Basal insulin use at baseline – No. (%) of patients</td>
<td>15 (22.7)</td>
<td>10 (14.7)</td>
<td>25 (18.7)</td>
</tr>
<tr>
<td>Basal insulin mean dose - units</td>
<td>29.6 (19.5)</td>
<td>29.6 (17.7)</td>
<td>29.6 (18.4)</td>
</tr>
</tbody>
</table>

Date are reported as mean (SD) or n (%) unless otherwise stated.
ITT = intention to treat

Efficacy

The primary efficacy end point was the change from baseline in glycated hemoglobin level at week 26. Mean glycated hemoglobin levels at week 26 were reduced from baseline by 0.64% in the liraglutide (Victoza®) group, whereas the levels increased by 0.42% in the placebo group (estimated treatment difference, −1.06%; 95% confidence interval [CI], −1.65 to −0.46; P<0.001). This finding showed the superiority of Liraglutide (Victoza®) to placebo. The estimated treatment difference at week 52 was −1.30%; 95% CI, −1.89 to −0.70).

Liraglutide (Victoza®) was also found to be superior to placebo in reducing fasting plasma glucose levels from baseline. The estimated treatment difference at week 26 was -1.88 mmol/L (-33.8 mg/dL); 95% CI -3.09 to -0.66, and the estimated treatment difference at week 52 was -1.81 mmol/L (-32.6 mg/dL); 95% CI -3.17 to -0.44. Additionally, 63.7% of the patients in the liraglutide (Victoza®) group, as compared with 36.5% in the placebo group, attained glycated hemoglobin levels of
less than 7.0% (P<0.001). Mean body weight decreased in both groups at week 26 (−2.3 kg with liraglutide (Victoza®) and −0.99 kg with placebo) but was maintained only with liraglutide (Victoza®) at week 52 (−1.91 kg with Liraglutide (Victoza®) vs. 0.87 kg with placebo). Very-low-density lipoprotein cholesterol levels were decreased more with liraglutide (Victoza®) than with placebo at week 26 (ratio of change between liraglutide (Victoza®) and placebo, 0.82; 95% CI, 0.72 to 0.94), as were triglyceride levels (ratio of change, 0.83; 95% CI, 0.72 to 0.95), but no differences were apparent at week 52. No between-group differences were seen in systolic and diastolic blood pressure at either time point.

Safety
There was a higher incidence of gastrointestinal adverse events in the liraglutide (Victoza®) group versus the placebo group especially in the initial 8 weeks. The percentage of patients who had hypoglycemic episodes and the incidence of hypoglycemia was higher with liraglutide (Victoza®) than with placebo. **There were no severe hypoglycemic episodes with liraglutide (Victoza®), and there was one severe episode in the placebo group in an insulin-treated patient.**

Most patients in both treatment groups had normal lipase and amylase values, and all had normal calcitonin levels overall during the 52 weeks. However, lipase levels were higher with liraglutide (Victoza®) than with placebo at week 26 (treatment ratio 1.20; 95% CI, 1.08 to 1.32) and at week 52 (treatment ratio, 1.11; 95% CI, 1.01 to 1.23), whereas amylase levels were similar in the two treatment groups at week 26 and week 52.

**Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease**

The LEADER trial (NCT01179048) was a multi-national, multi-center, placebo-controlled, double-blind trial conducted to assess the cardiovascular effect of liraglutide (Victoza®) when added to standard care in patients with type 2 diabetes.

In this study, 9340 patients with type 2 diabetes who had a glycated hemoglobin level of 7.0% or more were eligible if they either had not received drugs for this condition previously or had been treated with one or more oral antihyperglycemic agents or insulin or a combination of these agents. The major inclusion criteria were the following: age 50 years or more with at least one cardiovascular coexisting condition (coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney disease of stage 3 or greater, or chronic heart failure of New York Heart Association class II or III) or an age 60 years or more with at least one cardiovascular risk factor, as determined by the investigator (microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle–brachial index [the ratio of the systolic
blood pressure at the ankle to the systolic blood pressure in the arm] of less than 0.9).

**Patients were excluded if they had type 1 diabetes; had previously used GLP-1 receptor agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, pramlintide, or rapid-acting insulin; a familial or personal history of multiple endocrine neoplasia type 2 or medullary thyroid cancer; or they had an occurrence of an acute coronary or cerebrovascular event within 14 days before screening and randomization.**

Patients were randomly assigned in a 1:1 ratio to receive either 1.8 mg (or the maximum tolerated dose) of liraglutide (Victoza®) or matching placebo once daily. For patients who did not meet the recommended target for glycemic control (glycated hemoglobin level ≤7% or individualized target at the investigator’s discretion) after randomization, the addition of any antihyperglycemic agents except for GLP-1 receptor agonists, DPP-4 inhibitors, or pramlintide was permitted. Patients were scheduled for follow-up visits at months 1, 3, and 6 and every 6 months thereafter. The minimum planned follow-up was 42 months with a maximum of 60 months of receiving the assigned regimen and an additional 30 days of follow-up afterward.

**Baseline Characteristics**

The mean age was 64 years and the population was 64.3% male. The mean duration of type 2 diabetes was 12.8 years, the mean HbA1c was 8.7% and the mean BMI was 32.5 kg/m². A history of previous myocardial infarction was reported in 31% of randomized individuals, a prior revascularization procedure in 39%, a prior ischemic stroke in 11%, documented symptomatic coronary disease in 9%, documented asymptomatic cardiac ischemia in 26%, and a diagnosis of New York Heart Association (NYHA) class II to III heart failure in 14%. The mean eGFR at baseline was 79 mL/min/1.73 m² and 41.8% of patients had mild renal impairment (eGFR 60 to 90 mL/min/1.73m²), 20.7% had moderate renal impairment (eGFR 30 to 60 mL/min/1.73m²) and 2.4% of patients had severe renal impairment (eGFR < 30 mL/min/1.73m²).

At baseline, patients treated their diabetes with: diet and exercise only (3.9%), oral antidiabetic drugs only (51.5%), oral antidiabetic drugs and insulin (36.7%) or insulin only (7.9%). The most common background antidiabetic drugs used at baseline and in the trial were metformin, sulfonylurea and insulin. At baseline, cardiovascular disease and risk factors were managed with: non-diuretic antihypertensives (92.4%), diuretics (41.8%), statin therapy (72.1%) and platelet aggregation inhibitors (66.8%). During the trial, investigators could modify antidiabetic and cardiovascular medications to achieve local standard of care treatment targets with respect to blood glucose, lipid, and blood pressure, and manage patients recovering from an acute coronary syndrome or stroke event per local treatment guidelines.
The median time to exposure to liraglutide (Victoza®) or placebo was 3.5 years with the median daily dose of liraglutide (Victoza®) at 1.78 mg. The mean percentage of time that patients received the trial regimen was 84% for liraglutide (Victoza®) and 83% for placebo. There were 4,668 subjects in the liraglutide (Victoza®) group and 4,672 in the placebo group.

Efficacy

The primary endpoint, MACE, was the time to first occurrence of a three-part composite outcome which included: cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. Liraglutide (Victoza®) significantly reduced the occurrence of MACE. The primary composite outcome occurred in fewer patients in the liraglutide (Victoza®) group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority). Death from cardiovascular causes occurred in fewer patients in the liraglutide (Victoza®) group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P=0.007). The rate of death from any cause was also lower in the liraglutide (Victoza®) group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (hazard ratio, 0.85; 95% CI, 0.74 to 0.97; P=0.02). The frequencies of nonfatal myocardial infarction and nonfatal stroke were lower in the liraglutide (Victoza®) group than in the placebo group, although the differences were not statistically significant.

There were significant mean differences between the liraglutide (Victoza®) group and the placebo group in the change from baseline to 36 months in the following variables: weight loss was 2.3 kg (95% CI, 2.5 to 2.0) higher in the liraglutide (Victoza®) group, the systolic blood pressure was 1.2 mmHg (95% CI, 1.9 to 0.5) lower in the liraglutide (Victoza®) group, the diastolic blood pressure was 0.6 mmHg (95% CI, 0.2 to 1.0) higher in the liraglutide (Victoza®) group, and the heart rate was 3.0 beats per minute (95% CI, 2.5 to 3.4) higher in the liraglutide (Victoza®) group.

Safety

Adverse events leading to the permanent discontinuation of the trial regimen were more common with liraglutide (Victoza®) than with placebo driven by gastrointestinal disorders in the liraglutide (Victoza®) group. During the trial, fewer patients in the liraglutide (Victoza®) group were treated with hypoglycemic medications (insulin, sulfonylurea, and glinides) than in the placebo group. Severe hypoglycemia occurred in 114 patients in the liraglutide (Victoza®) group and in 153 in the placebo group (rate ratio, 0.69; 95% CI, 0.51 to 0.93).

The overall rates of benign or malignant neoplasms were higher in the liraglutide (Victoza®) group than in the placebo group, but the difference was not statistically significant. There were 13 participants with pancreatic cancer in the liraglutide...
(Victoza®) group and 5 in the placebo group. Medullary thyroid carcinoma occurred in no participants in the liraglutide (Victoza®) group and in 1 in the placebo group. Calcitonin levels over time were similar in the two groups. Acute pancreatitis occurred in 18 participants in the liraglutide (Victoza®) group and in 23 in the placebo group. The mean levels of serum amylase and lipase were higher in the liraglutide (Victoza®) group than in the placebo group. Acute gallstone disease was more common with liraglutide (Victoza®) than with placebo (in 145 vs. 90 patients), including severe events (in 40 vs. 31).

**Dosage Forms**

**Injection**

18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg.

Package Size - 2 pens

Package Size – 3 pens

**Special Considerations**

Prior to first use, liraglutide (Victoza®) should be stored in a refrigerator between 36°F to 46°F. Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze liraglutide (Victoza®) and do not use liraglutide (Victoza®) if it has been frozen. After initial use of the liraglutide (Victoza®) pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F) or in a refrigerator (36°F to 46°F). Keep the pen cap on when not in use. Liraglutide (Victoza®) should be protected from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the liraglutide (Victoza®) pen without an injection needle attached. **Always use a new needle for each injection to prevent contamination.** Discard liraglutide (Victoza®) 30 days after first use.

**Summary/Conclusion**

Liraglutide (Victoza®) is an effective treatment in managing type 2 diabetes with proven benefits including a decrease in HbA1c and glucose levels, weight loss, and a reduction in risk of major adverse cardiovascular events. Notably, liraglutide (Victoza®) is associated with a low risk of major hypoglycemia events compared to insulin secretagogues (e.g. sulfonylureas) and insulin. Liraglutide (Victoza®) is also straight-forward to dose with no renal or hepatic dosage adjustments. However, liraglutide (Victoza®) does have a high incidence of gastrointestinal side effects along with the potential increased risk of thyroid C-cell tumors, pancreatitis, and acute gallbladder disease. It also has a significant increased cost compared to
existing antidiabetic medications like thiazolidinediones (TZDs) or sulfonylureas (SU) and is administered subcutaneously.

Currently, liraglutide (Victoza®) is included in The American Diabetes Association (ADA) "Standards of Care in Diabetes" clinical practice recommendations as a second-line treatment option in those with increased ASCVD risk, those with a compelling need to minimize hypoglycemia, or those with a compelling need to minimize weight gain or promote weight loss. It may be safely used as monotherapy as well as concomitantly with metformin, insulin, or other antidiabetic agents.

**Recommendation**

Liraglutide (Victoza®) should be added to the formulary.

**Prepared By:**

Chelsea Griffin, PharmD Candidate 2020

**Reviewed By:**

Catherine Hall, PharmD, BCPP, BCACP
Clinical Pharmacist, San Antonio State Hospital
October 25, 2019
References


**Texas HHSC Psychiatric Executive Formulary Committee**

**NEW DRUG APPLICATION FORM**

For consideration of inclusion into the HHSC Psychiatric Drug Formulary

**Date:** 8-2-2019

**Name of practitioner submitting the application:** Jean Baemayr

**Name of entity with which the practitioner is associated by employment or contract (i.e., state hospital, state supported living center, state center, or local authority (state-operated community services (SOCS) or community MHMR center)):**

SH (PEFC)

**Information regarding new drug:**

<table>
<thead>
<tr>
<th><strong>Therapeutic Classification</strong></th>
<th>Urinary anticholinergic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic Name</strong></td>
<td>solifenacin</td>
</tr>
<tr>
<td><strong>Trade Name(s)</strong></td>
<td>Vesiccare</td>
</tr>
<tr>
<td><strong>Manufacturer(s)</strong></td>
<td>Astellas, multiple generics (Aurobindo, Teva, Watson, Zydus, etc.)</td>
</tr>
<tr>
<td><strong>Dosage Form(s)</strong></td>
<td>tablet</td>
</tr>
</tbody>
</table>

Explain the pharmacological action or use of this drug
Muscarinic antagonist/ urinary antispasmodic used to treat overactive bladder

Explain the advantages of this drug over those listed in the formulary:
Side effect profile, cost

State which drugs this new drug would replace or supplement:
darifenacin, oxybutynin, trosipium, tolerodine

*******************************************************************************

☐ application is approved ______________ n/a ______________________________

signature of chairman of facility pharmacy and therapeutics committee

OR

☐ application is appropriate and complete ______________ n/a ______________________________

signature of clinical/medical director or designee
Solifenacin (Vesicare™)

Classification:
Urinary anticholinergic/antimuscarinic

Pharmacology
Solifenacin is a competitive muscarinic receptor antagonist. It decreases the contractions of the bladder, increases residual urine volume, and decreases detrusor muscle pressure.1,2

Indication
Solifenacin is FDA approved for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.2

Pharmacokinetics 1,2

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>C_{max}: 3-8 hours&lt;br&gt;Bioavailability: ~90%&lt;br&gt;Food effects: insignificant</td>
</tr>
<tr>
<td>Distribution</td>
<td>Volume of distribution (Vd): 600L&lt;br&gt;Highly protein bound (98%) in human plasma, primarily to the alpha1-acid glycoprotein</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Predominately metabolized in the liver via N-oxidation and 4R-hydroxylation and eliminated by CYP3A4&lt;br&gt;Active metabolite: 4R-hydroxy solifenacin CYP3A4 substrate</td>
</tr>
<tr>
<td>Excretion</td>
<td>After a 26 day period of the administration of a 10mg dose, less than 15% was excreted unchanged in the urine and 22.5% was excreted in the feces&lt;br&gt;Fecal elimination: 22.5%&lt;br&gt;Renal elimination: 69.2%, unchanged &lt;15%&lt;br&gt;Half-life: 45-68 hours&lt;br&gt;Half-life for those with severe renal impairment increases by 1.6 fold whereas for those with moderate hepatic impairment increases by 2-fold</td>
</tr>
</tbody>
</table>

Dosage/Administration
The dose of solifenacin is 5 mg orally daily. If the 5 mg daily is well tolerated, may titrate to 10 mg oral daily. Administer with water, swallow the whole tablet, with no regards to food.1
If administered concomitantly with a strong CYP3A4 inhibitor, the dose should not exceed 5 mg per a day.

**Use in Special Population**

Safety and efficacy has not been established in the pediatric population.\(^1\)\(^2\)

In a clinical study the safety and effectiveness between the elderly and younger populations were similar but the Cmax, AUC and t\(_{1/2}\) were higher by 20-25% in the elderly population.\(^2\) In placebo-controlled studies, similar safety and efficacy were observed between older patients (> 65 years and > 75 years) and younger patients (< 65 years).\(^2\) Caution may be used because it is listed on the Beers Criteria.\(^2\)

A dose exceeding 5 mg per a day is not recommended for patients with severe renal impairment defined as CrCl less than 30 mL/min. For patients with severe renal impairment there is a 2.1 fold increase in the AUC and for the t\(_{1/2}\) there is a 1.6 fold increase.\(^1\)\(^2\)

A dose exceeding 5 mg per a day is not recommended for patients with moderate hepatic impairment (Child-Pugh B) as there is an increase of 2-fold in the t\(_{1/2}\) and a 35% increase in the AUC. For those patients with severe hepatic impairment (Child-Pugh B), this medication is not recommended.\(^1\)\(^2\)

Solifenacin is a pregnancy category C, therefore it should not be used unless the benefit outweighs the potential risk. There is no data on humans with the use of solifenacin in pregnant women to evaluate the associated risk of malformations or miscarriages. Additionally, solifenacin should be avoided in those who are nursing as it is unknown if it is excreted in human milk.\(^1\)

**Contraindication**

Solifenacin is contraindicated in patients with a history of hypersensitivity reaction to solifenacin or any of its components. It is also contraindicated in those with uncontrolled narrow-angle glaucoma or those with urinary or gastric retention.\(^1\)

**Precautions**

Anticholinergic drugs effect the central nervous system hence reports of headache, confusion, hallucinations, and somnolence. Therefore, monitoring for these effects is advised and patients should be counselled to avoid driving and operating heavy machinery until the effects on the patient are known.\(^1\)

Administer with caution in patients with clinically significant bladder outflow obstruction, in patients with decreased gastrointestinal motility, and in patients being treated with narrow-angle glaucoma.\(^1\)
There is an increased QT prolongation risk for those patients with a history of QT prolongation or when used with other medications known to prolong the QT interval. Caution should be used in these patients.¹

Solifenacin has been associated with swelling of the face, lips, tongue and larynx after the first dose or after multiple doses. It may become life-threatening therefore discontinuation and medical attention maybe necessary.²

Anaphylactic reactions have been rarely reported.¹

Due to the CNS effects of solifenacin, the Beers Criteria suggest that solifenacin should be avoided in the elderly with delirium or those at an increased risk of delirium, those with dementia, or those with cognitive impairment.²

**Adverse Effects**

These adverse effects were recognized during a 12-week randomized, placebo-controlled trial.

**Common Adverse Reactions¹**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Placebo</th>
<th>Solifenacin 5mg</th>
<th>Solifenacin 10mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>4.2%</td>
<td>10.9%</td>
<td>27.6%</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.9%</td>
<td>5.4%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>1.8%</td>
<td>3.8%</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

**Other Adverse Reactions¹**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Placebo</th>
<th>Solifenacin 5mg</th>
<th>Solifenacin 10mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>2%</td>
<td>1.7%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1%</td>
<td>1.4%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>1%</td>
<td>1.9%</td>
<td>1.2%</td>
</tr>
<tr>
<td>UTI</td>
<td>2.8%</td>
<td>2.8%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>0.6%</td>
<td>0%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.8%</td>
<td>1.9%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Lower limb edema</td>
<td>0.7%</td>
<td>0.3%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.1%</td>
<td>1%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Depression</td>
<td>0.8%</td>
<td>1.2%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Cough</td>
<td>0.2%</td>
<td>0.2%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.6%</td>
<td>1.4%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

During the clinical trials, 1.5% of the patients discontinued the trial due to dry mouth.¹
Postmarketing reports include: peripheral edema, angioedema, hypersensitivity reactions, headache, confusion, hallucinations, delirium, somnolence, QT prolongation, tachycardia, palpitations, decreased appetite, hyperkalemia, glaucoma, GERD, muscle weakness.\(^1\)

**Monitoring \(^2,^3\)**

Monitor for an improvement in symptoms consisting of incontinence, urgency and frequency, and an increase in the amount of urine excreted for efficacy.\(^2\) Addition monitoring includes those related to the central nervous system at the initiation of the medication or when there is an increase in dose.\(^3\) Creatinine clearance and hepatic function should also be monitored.\(^3\)

**Interactions \(^1,^2\)**

Solifenacin has the following clinically important drug interactions:

**Potent CYP3A4 inhibitors**
- Concomitant use of solifenacin with potent CYP3A4 inhibitors increases the AUC and \(C_{\text{max}}\).
- It is recommended that a dose of 5 mg daily should not be exceeded when administered with potent CYP3A4 inhibitors.

**CYP3A4 inducers**
- Solifenacin is a substrate of CYP3A4 so inducers may decrease the solifenacin concentration.

**QT Prolongation**
- Concomitant use of drugs that prolong the QT interval may add to the QT effect of solifenacin and increase the risk of cardiac arrhythmias.
- Avoid use of solifenacin in combination with other drugs known to prolong QT interval.

**Potassium**
- Concomitant use of potassium with solifenacin may result in risk of gastrointestinal lesions.

**Anticholinergics**
- Concurrent use of anticholinergics with solifenacin may increase the risk of anticholinergic side effects.

**Bupropion**
- Concurrent use bupropion with solifenacin may lower the seizure threshold.

**Scopolamine**
- Concurrent use of scopolamine with solifenacin may result in an increased risk of CNS adverse effects, intestinal obstruction & urinary retention.

**Efficacy \(^1\)**

Four clinical trials for solifenacin were conducted to study the efficacy and safety as the treatment for overactive bladder. These clinical trials were conducted over a 12 week period, double-blind, randomized, placebo-controlled, parallel group, and
multicenter. Inclusion criteria required patients to have symptoms of overactive bladder for at least 3 months.

In these studies, 3027 patients were randomized with 1811 receiving solifenacin and 1216 receiving the placebo. Half of the studies evaluated both the 5 mg and 10 mg whereas the other two studies only evaluated the 10 mg dose. 93% of the patients were Caucasian and 80% were female with the average age of 58 years old.

In all four of the clinical trials the primary endpoint was an average in the number of micturition within 24 hours from baseline to 12 weeks. The mean reduction in the number of micturitions per 24 hours was significantly greater with solifenacin 5 mg (2.3 micturition reduction) and 10 mg (2.7) compared to placebo (1.4).

The secondary endpoint was an average in change from baseline to 12 weeks in the number of incontinence episodes within 24 hours and an average of the amount of urine excreted. The mean reduction in the number of incontinence episodes per 24 hours was significantly greater with solifenacin 5 mg (1.5 episode reduction) and 10 mg (1.8) compared with placebo (1.1). The mean increase in the volume voided per micturition was significantly greater with solifenacin 5 mg (32.3 mL) and 10 mg (42.5 mL) compared with placebo (8.5 mL).

The efficacy was found to be similar across patient age and gender.

**Dosage Forms/Cost**

Many generic manufacturers are available and price reflects approximate average of available dosage forms.

AWP is for starting dose of each medication except solifenacin has both the 5 mg and 10 mg dosage pricing.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>AWP per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>solifenacin</td>
<td>5 mg</td>
<td>$13.87</td>
</tr>
<tr>
<td>solifenacin</td>
<td>10 mg</td>
<td>$13.87</td>
</tr>
<tr>
<td>darifenacin*</td>
<td>7.5 mg</td>
<td>$11.06</td>
</tr>
<tr>
<td>oxybutynin chloride*</td>
<td>5 mg</td>
<td>$3.39</td>
</tr>
<tr>
<td>trospium ER*</td>
<td>60 mg</td>
<td>$6.74</td>
</tr>
<tr>
<td>tolterodine ER*</td>
<td>4 mg</td>
<td>$9.54</td>
</tr>
</tbody>
</table>

*Medications currently on formulary
Special Considerations $^{1,2,3}$

| No boxed warnings.  
| Caution in the elderly as solifenacin can antagonize central and peripheral muscarinic receptors therefore potentially causing constipation, dry eyes, dry mouth, confusion, and urinary retention.  
| Pregnancy Risk Factor C |

Summary/Conclusion

Solifenacin is FDA approved for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency. The most common adverse effects consist of constipation, dry mouth, and blurred vision which are expected due to the antagonistic effects on the muscarinic receptors.

Recommendation

It is recommended to add solifenacin to the drug formulary due to its efficacy and safety for overactive bladder symptoms.

References


Prepared by:
Annayancy Esparza, Pharm D. candidate
Ben & Maytee Fisch College of Pharmacy
University of Texas at Tyler

Reviewed and Edited by:
Brittany Parmentier, PharmD, BCPS, BCPP
Ben & Maytee Fisch College of Pharmacy
University of Texas at Tyler