HHSC Psychiatric Executive Formulary Committee Minutes

The HHSC Psychiatric Executive Formulary Committee (PEFC) convened on August 2, 2019 in Room 125 - ASH Building 552. The meeting was called to order by Dr. Messer, Chair at 9:35 a.m.

<table>
<thead>
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<th>Members</th>
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<tr>
<td>Jean Baemayr, PharmD- secretary</td>
<td>✓</td>
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<tr>
<td>John Bennett, M.D.</td>
<td>✓</td>
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<td>Bonnie Burroughs, PharmD</td>
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<tr>
<td>Barbara Carroll, RN</td>
<td>✓</td>
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<tr>
<td>Ramona Gaston-McNutt, RN</td>
<td>✓</td>
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<tr>
<td>Catherine Hall, PharmD</td>
<td>✓</td>
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<tr>
<td>Jeanna Heidel, PharmD</td>
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<tr>
<td>Jeff Matthews, MD</td>
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<tr>
<td>Mark Messer, DO- Chair</td>
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<tr>
<td>David Moron, MD</td>
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<tr>
<td>Scott Murry, MD</td>
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<tr>
<td>Kenda Pittman, PharmD</td>
<td>Absent</td>
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<tr>
<td>Rishi Sawhney, MD</td>
<td>✓</td>
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<tr>
<td>Glenn Shipley, DO</td>
<td>✓</td>
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<tr>
<td>Ashton Wickramasinghe, MD</td>
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Guests Present: Ann Richards, PharmD, State Hospital System; Rania Kattura, PharmD, Clinical Pharmacist Austin State Hospital; Brittany Parmentier, PharmD, Clinical Assistant Professor, UT Tyler (by phone); Angela Babin, RPh, Director of Pharmacy Services, Harris County Center for Mental Health and IDD
Introduction and Other Information
Dr. Messer welcomed the committee members.

Ramona Gaston-McNutt, RN, MSN, Chief Nurse Executive at the Austin State Supported Living Center, will be replacing Cleveland Dunlap.

Dr. Brad Fitzwater, Medical Director, HHSC Substance Use Disorders, has been appointed as an ex-officio member of the committee.

Conflict of Interest
The committee members present did not reveal any issues with conflict of interest.

Review of Minutes of April 5, 2019
On a motion by Dr. Hall, seconded by Dr. Messer, the minutes of the April 5, 2019 meeting were approved as previously distributed.

Unfinished Business

Psychotropic Medication Utilization Parameters for Children & Youth
(April 2018)
The Psychotropic Medication Utilization Parameters for Children and Youth in Texas Public Behavioral Health was distributed to the systems academic partners (University of Texas, Texas A&M, and Texas Tech facilities) for review on March 4, 2019, with an April 5, 2019 due date to return any comments. All comments received were forwarded back to the Psychotropic Medication Utilization Parameters for Children & Youth workgroup. The final draft document was sent to PEFC members for an email vote on June 10, 2019. Receiving no negative votes, the final document was approved and was posted to the PEFC website on July 26. The posted document is undergoing formatting revisions by the accessibility team in order to meet the requirement to become accessible within 90 days of posting.

This document replaces the previous document from 2016. Dr. Muse encouraged the committee members to distribute the link to the document on the PEFC website:


TAC Title 25, Part 1, Chapter 415, Subchapter C (April 2017)
The required Rulemaking Notification Form (RNF) has been approved by the Rules Coordination Office. A workgroup representing state hospitals, state supported living centers, and community centers, was proposed:

Jean Baemayr, PharmD, State Hospitals
Ann Richards, PharmD, State Hospitals
Mark Messer, DO, State Hospitals
Rishi Sawhney, MD, Community Behavioral Health
Kenda Pittman, PharmD, State Supported Living Centers
Bonnie Burroughs, PharmD, State Supported Living Centers
John Bennett, MD, Local Behavioral Health Centers
Angela Babin, RPh, Local Mental Health Centers

On a motion by Dr. Sawhney, seconded by Dr. Messer, the committee approved the formation of a PEFC workgroup comprised of the members listed above to revise the TAC.

The workgroup will prepare a draft of recommended revisions to be presented at the next PEFC meeting.

**Psychotropic Audit Criteria & Guidelines Review-Antidepressants**
(April 2012)

1. The committee reviewed the use of the statement “as clinically indicated” in the audit criteria and audit checklist. The committee determined that the use of this phrase was appropriate to include in the audit criteria and audit checklist.

2. The committee reviewed the criteria “BNP every 3 months or as clinically indicated” for clozapine use and determined that “BNP as clinically indicated based on cardiac risk factors” would provide greater clarification of when this test should be used.

On a motion by Dr. Bennett, seconded by Dr. Messer, this clarification was approved. The clozapine audit criteria and checklist documents will be updated and posted on the PEFC website.

3. The committee reviewed newly revised audit criteria and audit checklist templates. The documents were modified to meet ADA accessibility standards.

On a motion by Dr. Messer, seconded by Dr. Bennett, the templates were approved for use.

4. The committee reviewed newly revised audit criteria and guidelines for:
   - Amoxapine
   - Bupropion
   - Clomipramine
   - Duloxetine
   - Esketamine
   - Mirtazapine
   - Monoamine oxidase inhibitors (phenelzine and tranylcypromine)
   - Nefazodone
   - SSRIs
Trazodone
Tricyclic antidepressants
Venlafaxine

A workgroup comprised of Dr. Messer, Dr. Parmentier, Dr. Hall, and Dr. Richards used information from Micromedex, Lexicomp, AHFS, and manufacturer package inserts to update the audit material.

On a motion by Dr. Bennett, seconded by Dr. Messer, the revised antidepressant audit criteria and guidelines & audit checklists were approved as modified with additional input from the committee. The updated documents will be posted to the PEFC website.

**GLP-1 Agonist Review** (April 2018)

Dr. Hall presented a comparison of available GLP-1 agonist products.

On a motion by Dr. Messer, seconded by Dr. Bennett, the committee will consider the addition of liraglutide (Victoza®) at the next meeting. Dr. Hall will prepare the monograph.

**New Business**

**New HHSC Psychiatric Executive Formulary Committee Website**

The PEFC website is live:

https://hhs.texas.gov/about-hhs/leadership/advisory-committees/psychiatric-executive-formulary-committee

An email was sent out to committee members advising them of the new address on June 3, 2019.

**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: Olanzapine/hypertriglyceridemia**

A 44-year-old female was admitted to a state hospital from jail with a diagnosis of schizophrenia and substance use disorder (methamphetamine). She was not reported to be on medications while in jail. This is her second admission to the state hospital, and she had been discharged on aripiprazole 10 mg daily after her first admission.

Admission labs were normal except: ALT 9 IU/L, BUN/Scr ratio 27, triglycerides 192 mg/dL, HDL 32 mg/dL, RBC 3.97 million/mcL, Hgb 10.5 g/dL, Hct 32.7%, MCH 26.5 pg, monocytes 0.8 10⁹/L, and eosinophils 3.1 10⁹/L. She did not receive any STAT
doses of medications, although she did receive one court ordered IM back-up dose of olanzapine 10 mg upon refusal to take oral medication on day 49. She was started on olanzapine 5 mg daily at bedtime on day one of hospitalization, increased to 10 mg daily at bedtime on day 29, increased to 15 mg daily at bedtime on day 40, increased to 10 mg twice daily on day 50, increased to 5 mg daily in the morning and 20 mg daily at 5pm on day 61, with final increase to 5 mg daily in the morning and 25 mg daily at 5pm on day 104.

Labs done on day 115 showed an abnormal lipid panel: Cholesterol 258 mg/dL, triglycerides 1536 mg/dL, HDL 23 mg/dL, and LDL unable to be calculated due to triglycerides being greater than 400 mg/dL. At the time, the patient was taking olanzapine, ferrous gluconate, multivitamin, vitamin C and docusate. She did not experience any symptoms of pancreatitis; no abdominal pain was noted at any point. She also did not experience any nausea or vomiting.

After being tapered off olanzapine her labs on day 133, 18 days later showed a decrease to: Cholesterol 186 mg/dL, triglycerides 497 mg/dL, HDL 28 mg/dL, LDL unable to be calculated due to triglycerides being greater than 400 mg/dL. Aripiprazole was initiated, as well as fish oil (omega-3 fatty acids) 4 capsules once daily. A low fat, low cholesterol diet was also started.

Olanzapine is considered to have high risk for metabolic syndrome, which is defined as a patient having 3 or more of the following: increases in waist circumference, blood pressure, blood sugar, triglycerides, and low-density lipoprotein (LDL) cholesterol (Ther Clin Risk Manag. 2017;13:757-777). Olanzapine has been shown to lead to extreme body mass index (BMI) increases due to its high affinity for the 5HT2C receptor, which causes the side effects of weight gain and metabolic syndrome. Other antipsychotics with high affinity for the 5HT2C receptor are asenapine, clozapine, sertindole and ziprasidone. Olanzapine has also been shown in case reports to lead to increased triglycerides, cholesterol and LDL. It is noted from these reports that marked decreases in the above are seen after cessation of olanzapine (J Clin Med Res. 2012;4(3):206-208; ACG Case Rep J. 2016;3(4):1-3).

The lipid panel on the 115th day of hospitalization showed significant increases in cholesterol, LDL and triglycerides compared with her baseline on admission. This change is likely due to olanzapine and probably increased in severity as the olanzapine dose was titrated up. Repeat lipid panel after discontinuing olanzapine showed significant decreases in cholesterol and triglycerides. Therefore, it is highly likely olanzapine caused the lipid panel abnormalities. While other antipsychotics are implicated in elevated triglycerides, it is reasonable to initiate aripiprazole as it is considered lowest risk for causing metabolic syndrome. It has a lower affinity for the receptor known to lead to these changes. Rechecking lipid panel after initiation of aripiprazole is recommended as there are some case reports that attribute hypertriglyceridemia with aripiprazole use.
**ADR: Valproate/eosinophilia**

A 39-year-old AAF with schizoaffective disorder bipolar type and IDD was admitted to a state hospital from a state supported living center. At admission, lipids, CBC (eosinophils 0.1 10^9/L, WBC 4.8 10^9/L), CMP, and T4 were wnl; TSH was 0.23 mU/L. Multiple oral and long acting antipsychotic medications had been administered over the previous month prior to arrival including paliperidone, aripiprazole and fluphenazine. At admission, all antipsychotics except fluphenazine 5 mg twice daily were discontinued. Oxcarbazepine 300 mg twice daily and lorazepam 1.5 mg twice daily were continued along with other medical medications including levothyroxine and simvastatin for hypothyroidism and dyslipidemia.

After admission fluphenazine was tapered and discontinued over 4 days. Valproic acid 500 mg twice daily was started approximately 1 week after admission. Lithium carbonate 450 mg twice daily was added approximately 2 weeks after admission. One month after admission oxcarbazepine was tapered and discontinued, lithium was increased to 600 mg twice daily and valproic acid was increased to 750 mg twice daily. At this time a CBC indicated a mild increase in eosinophils at 1.1 10^9/L. Five weeks after admission paliperidone 3 mg daily was added. She began to have elevated WBC of 20.4 10^9/L, eosinophils of 3.1 10^9/L and low-grade temp of 99.4°F and she was transferred to a local medical hospital. She was treated for a vaginal infection with a course of cephalexin 500 mg four times daily for a week. After return from the medical hospital her eosinophils continued to remain elevated with a peak eosinophil count of 9.1 10^9/L with WBC of 17 10^9/L approximately 6 weeks after admission. The valproic acid level was 68.1 mcg/mL around that time. She was noted to have severe eosinophilia, but was asymptomatic for other systemic symptoms at this time with normal temperature, no edema, rash, pain or discomfort noted. Valproic acid was decreased to 750 mg daily and then discontinued over the next 3 days. Eosinophils then improved to 4.6 10^9/L, but WBC was elevated at 13.6 10^9/L with automated ANC wnl at 2.4 10^9/L. A UA was obtained and treatment with amoxicillin was initiated for strep B UTI. Paliperidone was increased to 6 mg daily. A repeat CBC noted eosinophils 5.1 10^9/L and WBC 14.8 10^9/L with valproic acid level less than 10 mcg/mL. Eosinophils improved from the peak of 9.1 10^9/L after discontinuation of valproic acid, but did not normalize by the time of discharge with last CBC noting eosinophils of 5.9 10^9/L and WBC 14.3 10^9/L with CMP remaining wnl throughout the admission. She remained on lithium, lorazepam and paliperidone in addition to her medical medications of levothyroxine and simvastatin. A consultant hematologist suspected the elevation in eosinophils to be drug-induced secondary to valproic acid and reported the eosinophils should continue to improve over the next 1-2 months.

Of note this patient had a history of treatment with valproate in the past without reported hypersensitivity reaction. Typical onset of eosinophilia with valproate treatment is within 40 days of initiation of therapy which correlates with the time frame of the elevation in eosinophils in this patient (Micromedex®). Early signs of
hypersensitivity may occur without a rash or other organ system involvement as typically seen with drug reaction with eosinophilia and systemic symptoms (DRESS) (lymphadenopathy, hepatitis, nephritis). Leukocytosis and mild fever were noted although there were also confounding vaginal and subsequent urinary tract infections noted around this time as well. The primary provider noted that aside from the elevation in eosinophils, the patient was asymptomatic for systemic symptoms. The hematologist suspected this was likely drug-induced eosinophilia caused by valproate.

**ADR: Alendronate/esophagitis**

On 4/27/19, a patient underwent surgery at the community hospital to fix a compression fraction of the hip. She was at a rehabilitation facility from roughly 5/1/19 to 5/21/19. At the time of her surgery, her medications were atorvastatin 10 mg daily, chlorthalidone 25 mg daily (since 3/12/19), mirabegron ER 25 mg daily at bedtime, PEG 17 grams daily, solifenacin 5 mg daily at bedtime, and vitamin D 1,000 International Units daily.

On 5/21/19, she returned to the state hospital and was restarted on the medications above. She was ambulating with a walker and participating in physical therapy; enoxaparin 30 mg subq had been discontinued on 5/20/19. On 5/25/19, alendronate 70 mg once weekly was started—she received doses on 5/25 and 6/1. The order contained the following instruction: TAKE ON SATURDAY MORNINGS AT 6:30AM- NO FOOD/DRINK AN HOUR PRIOR OR AFTER. DRINK WITH WATER ONLY. MUST SIT UPRIGHT IN THE LOBBY FOR 30 MIN AFTER TAKING IT

On 5/29/19, she was seen by one of the medical physicians because of chest pain that she associated with a big pink pill. The pain was located in midline substernally and she had the sensation that the pill was stuck in her throat. The physician’s note mentioned CVS: S1, S2, regular; EKG normal sinus rhythm. No significant ST-T changes suggestive of ischemia. Cardiac angiogram in May 2016 had revealed normal coronary arteries. The pain was thought to be due to her calcium carbonate pill and this was switched to a suspension.

On 5/30/19, she continued to complain of sore throat, difficulty swallowing, shortness of breath, and weakness. She was eating and drinking very little. Mild erythema of posterior pharyngeal was noted and a throat culture was ordered (wnl). She received pink magic mouthwash. On 6/3/19, she continued to complain of sore throat and weakness. Acetaminophen and Cepacol were ordered. Later that day, she was sent to the medical hospital because of an oxygen saturation level of 80% on room air. Oxygen saturation was 100% on O2 mask prior to going to the hospital. At the ER, they found that her potassium = 2.7 meq/L (on 3/28/19, K was 3.8 meq/L). The cardiologist ruled out cardiac problems and pulmonary embolism.

On 6/4, she returned to the state hospital with a diagnosis of hypokalemia. The doctor at the community hospital told the receiving medical physician at the state hospital...
hospital that she had strep throat and she returned with a five-day prescription for Augmentin. Alendronate 70 mg, chlorthalidone 25 mg daily, and solifenacin 5 mg daily at bedtime were discontinued. After a couple of days, she stopped complaining of a sore throat and her intake improved. On 6/18/19, potassium was 4.3 meq/L. Her current medications are atorvastatin 10 mg daily at bedtime, calcium carbonate 500 mg twice daily, mirabegron ER 25 mg daily at bedtime, PEG 17 grams daily, and vitamin D 1,000 International Units daily. Over the past week, systolic blood pressure has ranged from 119-140 mm Hg, diastolic blood pressure from 64-86 mm Hg, and pulse from 63-88 beats per minute.

**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.

The committee reviewed a new template for drug monographs. The template is designed to create ADA-accessible uniformity in the information presented in drug monographs.

On a motion by Dr. Bennett, seconded by Dr. Messer, it was recommended to adopt the template for use in future monographs.

*Cannabidiol (Epidiolex®) - pended until the next meeting.*

*Pimavanserin (Nuplazid®) - presented by Dr. Richards*

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

On a motion by Dr. Messer, seconded by Dr. Hall, the committee declined to add pimavanserin (Nuplazid®) to the formulary.

*Losartan (Cozaar®) – presented by Dr. Parmentier*

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

On a motion by Dr. Bennett, seconded by Dr. Messer, it was recommended to add losartan to the formulary. The formulary check list was completed and no issues were detected.

**Angiotensin Receptor Blocker Review**

Dr. Parmentier presented a review of available ARB products.

The committee discussed moving olmesartan and valsartan from reserve status to regular status and adding a new category for angiotensin receptor blockers in the cardiovascular section of the formulary.
On a motion by Dr. Messer, seconded by Dr. Baemayr, it was recommended to move valsartan from reserve use status to regular formulary status under the new category of angiotensin receptor blockers. Losartan will also be added to this category. Olmesartan will remain in reserve use status with the guideline “In case of drug shortages” added to the current guideline of “Prior failure to ACE inhibitor therapy due to intolerable side effects.”

**Hepatitis C Drug Purchases**

For the third quarter of fiscal year 2019 (March 2019-May 2019), the following purchases for drugs to treat hepatitis C were made:

State Hospitals: $96,324.95
State Supported Living Centers: $31,764.48

**Quarterly Non-Formulary Drug Justification Report**

For the first through third quarters of fiscal year 2019, only the State Hospitals reported use of non-formulary agents. The SSLC facilities 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:

- losartan (Cozaar®) - added at today’s meeting.
- solifenacin (Vesicare®) - a monograph will be reviewed at the next meeting.
- sofosbuvir/velpatasvir (Epclusa®)
- magnesium oxide
- sitagliptin (Januvia®)

**Drug Deletions**

The committee did not consider any drug deletions not already specified in the sectional review.

**New Dosage Forms**

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

**Drug Formulary Sectional Review:**

In reviewing the formulary drug listings for dermatologicals (acne agents through burns agents), Dr. Hall made the following recommendation:

Antihistamine Agents - delete doxepin

On a motion by Dr. Messer was approved and the formulary will be updated.
Issues from the Medical Director, State Hospital System

Dr. Muse discussed forming a workgroup to develop psychotropic medication utilization parameters for adults. Dr. Sawhney was asked to serve as co-chair, along with Dr. Muse. Dr. Richards expressed an interest in participating in the workgroup.

Dr. Muse discussed the use of rating scales to measure treatment outcomes. She would like to include rating scales in the psychotropic medication utilization parameters for adults document.

On a motion by Dr. Messer, seconded by Dr. Sawhney, the committee approved the formation of the workgroup. The committee also approved the incorporation of rating scales into the draft document, which will be brought back to the committee for final review and approval before being distributed.

Issues from the Medical Director, State Supported Living Centers

Dr. Shipley reported that Dr. Taylor is retiring at the end of the month.

FDA Drug Recalls and Safety Communications

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

Angiotensin receptor blockers

Continued/expanded recalls due to the presence of impurities. Below is a link to an FDA web site that lists the “FDA's Assessment of Currently Marketed ARB Drug Products”


Generic ophthalmic ointments distributed by Perrigo

Various lots of the following were recalled due to the potential for non-sterility as noted by “management concerns regarding the sufficiency of Quality Assurance controls over critical systems in the manufacturing facility.”

- Neomycin and Polymixin B and Bacitracin Zinc Ophthalmic Ointment
- NEO-POLY DEX (Neomycin and Polymixin B and Dexamethasone) Ophthalmic Ointment
- NEO-POLYCIN HC (Neomycin and Polymixin B and Bacitracin Zinc and Hydrocortisone Acetate) Ophthalmic Ointment
- POLYCIN (Polymyxin B and Bacitracin Zinc) Ophthalmic Ointment
- Bacitracin Ophthalmic Ointment
- Sulfacetamide Sodium Ophthalmic Ointment
- Puralube Ophthalmic Ointment
The FDA has issued the following safety communication that may affect our facilities:

**“Z” drugs and dangerous sleep behaviors**

The Food and Drug Administration (FDA) is advising that rare but serious injuries have happened with certain common prescription insomnia medicines because of sleep behaviors, including sleepwalking, sleep driving, and engaging in other activities while not fully awake. These complex sleep behaviors have also resulted in deaths. These behaviors appear to be more common with eszopiclone (Lunesta), zaleplon (Sonata), and zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist) than other prescription medicines used for sleep.

As a result, a Boxed Warning, the FDA’s most prominent warning, will be required to be added to the prescribing information and the patient Medication Guides for these medicines. Also required is a Contraindication, the strongest warning, to avoid use in patients who have previously experienced an episode of complex sleep behavior with eszopiclone, zaleplon, and zolpidem. Serious injuries and death from complex sleep behaviors have occurred in patients with and without a history of such behaviors, even at the lowest recommended doses, and the behaviors can occur after just one dose. These behaviors can occur after taking these medicines with or without alcohol or other central nervous system depressants that may be sedating such as tranquilizers, opioids, and anti-anxiety medicines.

The CDC has issued the following Health Advisory that may affect our facilities:

**Nationwide Shortage of Tuberculin Skin Test Antigens**

The CDC is expecting a 3 to 10 month nationwide shortage of Aplisol, a product of Par Pharmaceuticals, and one of two purified-protein derivative (PPD) tuberculin antigens licensed by the Food and Drug Administration (FDA) for use in performing tuberculin skin tests (TSTs). The CDC recommends the following three general approaches to mitigate a reduction in TB testing capability resulting from the expected shortage of Aplisol:

- Substitute interferon-gamma release assay [IGRA] blood tests for TSTs.
- Substitute Tubersol for Aplisol for skin testing.
- Prioritize allocation of TSTs, in consultation with state and local public health authorities. Prioritization might require the deferment of testing some persons.

Annual TB testing of health care personnel is not recommended unless there is a known exposure or ongoing transmission.

**News Briefs**

The following information was shared with the committee members:
Texas Becomes First State Where Naloxone Is Sold Online

The Dallas Morning News (5/19, Sarder) reports that “with opioid-related deaths on the rise each year in the U.S., Texas has become the first state to offer” naloxone, an opioid antagonist, “online, freeing users of the stigma associated with drug use.” Texas is a “pilot state for Fiduscript’s Naloxone Exchange, which intends to launch in other states in a few months, though there is no hard timeline yet.” So far, “the company has secured direct or indirect approvals from 25 states including Texas.”

Trimethoprim-Sulfamethoxazole linked To Severe Acute Respiratory Distress Syndrome In Five Previously Healthy Teenagers

CHEST Physician (5/29, Splete) reports researchers have linked TMP-SMX “to severe acute respiratory distress syndrome (ARDS). in five previously healthy teens, two of whom died.” The findings were published in a case series in Pediatrics. The majority of the children were prescribed TMP-SMX for the treatment of acne.

Texas Legislature Passes Bill Limiting Opioid Prescriptions For Acute Pain

The Austin (TX) American Statesman (5/30, Huber, Subscription Publication) reports that “Texas lawmakers last week gave final approval to a bill that will limit opioid prescriptions for acute pain to a 10-day supply.” The “limits will not apply to those who are receiving opioids for chronic pain, cancer or end-of-life care.” The legislation “also requires that all opioid prescriptions be sent to pharmacies electronically to cut down on the number of fraudulent written prescriptions.”

Gabapentinoids May Increase Users’ Risk For Suicidal Behavior, Unintentional Overdoses, Injuries, And Car Accidents

Reuters (6/17, Harding) reports that gabapentinoids appear to increase “users’ risks for suicidal behavior, unintentional overdoses, injuries and car accidents – and the risks are particularly high for teens and young adults,” researchers concluded after examining “Swedish registry data on 191,973 people age 15 and older prescribed pregabalin or gabapentin in 2006-2013.” The findings were published online June 12 in the BMJ.

Open Forum

No items.

Next Meeting Date

The next meeting is scheduled for October 25, 2019.

Adjourn

There being no further business, the meeting was adjourned at 3:00 p.m.
Approved:  

Mark Messer, D.O.

Mark Messer, D.O., Chairman

Minutes Prepared by:

Jean Baemayr, PharmD

Appendix

Appendix A – pimavanserin (Nuplazid®) New Drug Application and monograph
Appendix B – Iosartan (Cozaar®) New Drug Application and monograph
Texas HHSC Psychiatric Executive Formulary Committee
NEW DRUG APPLICATION FORM

For consideration of inclusion into the HHSC Psychiatric Drug Formulary

Date: __May 28, 2019__

Name of practitioner submitting the application: __Nina Jo Muse, MD__

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)):

__State Hospital System, Chief Medical Officer__

Information regarding new drug:

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<thead>
<tr>
<th>Therapeutic Classification</th>
<th><strong>antipsychotic</strong></th>
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<tr>
<td>Generic Name</td>
<td>pimavanserin</td>
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<tr>
<td>Trade Name(s)</td>
<td>Nuplazid</td>
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<tr>
<td>Manufacturer(s)</td>
<td>Acadia Pharmaceuticals</td>
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<td>Dosage Form(s)</td>
<td>34mg capsules</td>
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Explain the pharmacological action or use of this drug

FDA approved to treat hallucinations and delusions in Parkinson’s Disease

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

May have efficacy in treatment resistance or refractory schizophrenia in place of or in addition to clozapine.

State which drugs this new drug would replace or supplement: __clozapine__

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

☐ 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__

____________________________________________________

Texas Health and Human Services • hhs.texas.gov
### Pimavanserin (Nuplazid®)

**Classification:**
Atypical antipsychotic

**Pharmacology**

The development of Parkinson’s Disease Psychosis likely involves multiple systems including dopamine, glutamatergic, cholinergic, and serotonergic systems. More than half of all patients with Parkinson’s disease eventually develop psychotic symptoms over the course of their disease.¹ It has been hypothesized that dopamine deficiency precipitates up-regulation of 5-HT function and receptor sensitivity, especially in the visual processing circuitry. This can lead to psychosis with prominent visual hallucinations, with many patients having insight.² Pimavanserin’s mechanism of action in the treatment of hallucinations and delusions associated with Parkinson’s disease psychosis is thought to be mediated through a combination of inverse agonist and antagonist activity at serotonin 5-HT2A receptors and to a lesser extent at serotonin 5-HT2C receptors.³ Pimavanserin is a selective serotonin inverse agonist with no appreciable binding affinity for dopamine, histamine, adrenergic, or muscarinic receptors. The proposed mechanism of action could be mediated through a combination of inverse agonist and antagonist activity at serotonin 5-HT2A receptors and to a lesser extent serotonin 5-HT2C receptors. At its therapeutic dose of 34 mg, pimavanserin does not bind to dopamine (included D2), histamine, muscarinic or adrenergic receptors. Pimavanserin is an inverse agonist that selectively inhibits the basal or constitutive activity of the 5-HT2A receptors thus suppressing the basal or constitutive activity of the receptors. As an antagonist, pimavanserin blocks ligand stimulation of the receptors but permits basal or constitutive activity. As an inverse agonist and an antagonist, pimavanserin inhibits the stimulation of the 5-HT2A receptors and to a lesser degree the 5-HT2C receptors and suppresses their basal or constitutive activity. Overall, pimavanserin decreases the activity of the 5-HT2A receptors and to a lesser extent 5-HT2c receptors to even below baseline levels.

**Indication**

The FDA labeling shows that pimavanserin is indicated for the treatment of hallucinations and delusions associated with Parkinson’s disease psychosis.³
### Pharmacokinetics\(^{3,4}\)

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<th><strong>Absorption</strong></th>
<th>Median (T_{\text{max}}) was 6 hours (range 4-24) and generally unaffected by dose.</th>
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<tr>
<td></td>
<td>Bioavailability of pimavanserin oral tablet and pimavanserin oral solution (not commercially available) was essentially identical.</td>
</tr>
<tr>
<td></td>
<td>Formation of the major circulating (N)-desmethylated metabolite AC-279 (active) from pimavanserin occurs with a median (T_{\text{max}}) 6 hours.</td>
</tr>
<tr>
<td></td>
<td>Ingestion of a high-fat meal had no significant effect on rate ((C_{\text{max}})) and extent (AUC) of pimavanserin exposure. (C_{\text{max}}) decreased by about 9%; AUC increased by about 8% with a high-fat meal.</td>
</tr>
<tr>
<td></td>
<td>Administration of one 34 mg capsule once daily results in plasma pimavanserin concentrations that are similar to administration with two 17 mg tablets once daily.</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Highly protein bound (~95%) in human plasma.</td>
</tr>
<tr>
<td></td>
<td>Protein binding appeared to be dose-independent and did not change significantly over dosing time from Day 1 to Day 14.</td>
</tr>
<tr>
<td></td>
<td>Volume of distribution 2,173 L ± 307 after single dose pimavanserin 34 mg.</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Predominately metabolized by CYP3A4 and CYP3A5 and to a lesser extent by CYP2J2, CYP2D6, and various other CYP and FMO (flavin-containing monooxygenase) enzymes.</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 is the major enzyme responsible for the formation of its major active metabolite (AC-279).</td>
</tr>
<tr>
<td></td>
<td>Pimavanserin does not cause clinically significant CYP inhibition or induction of CYP3A4.</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>After a 34 mg dose, approximately 0.55% of pimavanserin was eliminated as unchanged drug in the urine and 1.53% was eliminated in the feces after 10 days.</td>
</tr>
<tr>
<td></td>
<td>Pimavanserin half-life – ~57 hours; AC-279 half-life – ~200 hours</td>
</tr>
</tbody>
</table>
**Dosage/Administration**

The dose of pimavanserin is 34 mg orally daily, without titration. It can be administered with or without food.\(^3\)

If administered concomitantly with a strong CYP3A4 inhibitor, the dose should be reduced to 10 mg orally daily.\(^3\)

Avoid concomitant use of strong or moderate CYP3A4 inducers with pimavanserin.\(^3\)

**Use in Special Population**

Safety and efficacy have not been established in children younger than 18 years.\(^3\)

No dose adjustment is required for elderly patients.\(^3\)

No dosage adjustment for pimavanserin is needed in patients with mild to severe renal impairment or end stage renal disease. However, pimavanserin should be used with caution in patients with severe renal impairment and end stage renal disease.\(^3\)

No dosage adjustment for pimavanserin is recommended in patients with hepatic impairment.\(^3\)

There is no data on pimavanserin use in pregnant women that would allow assessment of the drug-associated risk of major congenital malformations or miscarriage. There is no information regarding the presence of pimavanserin in human milk, the effects on the breastfed infant, or the effects on milk production.\(^3\)

**Contraindication**

Pimavanserin is contraindicated in patients with a history of hypersensitivity reaction to pimavanserin or any of its components.\(^3\)

**Precautions**

Antipsychotic drugs increase the risk of death in elderly patients with dementia-related psychosis. (Boxed warning)\(^3\)

QT prolongation has been reported with pimavanserin. Pimavanserin should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), certain
antipsychotics (e.g., ziprasidone, chlorpromazine, thioridazine), and certain antibiotics (e.g., gatifloxacin, moxifloxacin).³

Pimavanserin should be avoided in patients with a history of cardiac arrhythmias; other circumstances that may increase the risk of the occurrences of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia; and the presence of congenital prolongation of the QT interval.³

**Adverse Effects**

Common Adverse Reactions (incidence ≥ 5% and at least twice the rate of placebo)³

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Pimavanserin 34 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral edema</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>Confusional state</td>
<td>6%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Adverse Reactions in Placebo-Controlled Studies of 6-Week Treatment Duration and Reported in ≥ 2% and > Placebo³

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Pimavanserin 34 mg (N=202)</th>
<th>Placebo (N=231)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Constipation</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
## Adverse Effect

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Pimavanserin 34 mg (N=202)</th>
<th>Placebo (N=231)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucination</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Confusional state</td>
<td>6%</td>
<td>3%</td>
</tr>
</tbody>
</table>

During the clinical trials, 8% (16/202) pimavanserin patients and 4% (10/231) placebo patients discontinued the trial due to adverse reactions. The adverse reactions that occurred in more than one patient and with an incidence at least twice the placebo were hallucinations (2% pimavanserin vs. <1% placebo), urinary tract infections (1% pimavanserin vs. <1% placebo), and fatigue (1% pimavanserin vs. 0% placebo).³

Postmarketing reports include: somnolence, falls, rash, urticaria, and reactions consistent with angioedema (e.g., tongue swelling, circumoral edema, throat tightness, and dyspnea).³

## Monitoring

Monitor for an improvement in the frequency or severity of hallucinations or delusions in patients with Parkinson disease psychosis as this indicates efficacy.⁴

Even though preliminary research indicates tolerability to pimavanserin and the manufacturer does not require specific monitoring, it is recommended that the atypical audit criteria monitoring parameters be followed.

## Interactions

Pimavanserin has the following clinically important drug interactions:

**QT Prolongation**³,⁴

- Concomitant use of drugs that prolong the QT interval may add to the QT effect of pimavanserin and increase the risk of cardiac arrhythmias.
- Avoid use of pimavanserin in combination with other drugs known to prolong QT interval.
- Examples include: Class 1A antiarrhythmics (quinidine, procainamide, disopyramide); Class 3 antiarrhythmics (amiodarone, sotalol); Antipsychotics
(ziprasidone, chlorpromazine, thioridazine); Antibiotics (gatifloxacin, moxifloxacin)

**Strong CYP3A4 Inhibitors**

- Concomitant use of pimavanserin with a strong CYP3A4 inhibitor increases pimavanserin exposure.
- If pimavanserin and a strong CYP3A4 inhibitor are used concomitantly, reduce the dosage of pimavanserin to 10 mg/day.
- Examples include: itraconazole, ketoconazole, clarithromycin, indinavir

**Strong or Moderate CYP3A4 Inducers**

- Concomitant use of pimavanserin with a strong or moderate CYP3A4 inducers reduces pimavanserin exposure
- Avoid concomitant use of strong or moderate CYP3A4 inducers with pimavanserin
- Examples include: Strong inducers – carbamazepine, St. John’s Wort, phenytoin, rifampin; Moderate inducers – modafinil, thioridazine, efavirenz, nafcillin

**Efficacy**

Measuring Parkinson’s Disease Psychosis (PDP) is challenging due to the lack of widely used, validated PDP rating scales. Scales in non-PDP conditions (such as schizophrenia) have been used even though the clinical picture between disease states are different. The Movement Disorder Society established a Task Force on Rating Scales in Parkinson’s Disease that reviewed rating scales used in PDP. This Task Force noted that different scales may be better in some settings versus other settings. Since no scale could be identified as being ideal, this Task Force recognized some scales as being recommended and others as suggested for use in PDP. Recommended scales include: Neuropsychiatric Inventory (NPI); Brief Psychiatric Rating Scale (BPRS); Positive and Negative Syndrome Scale (PANSS) and Schedule for Assessment of Positive Symptoms (SAPS).

**Parkinson’s Disease Psychosis**

After three failed trials, Acadia Pharmaceuticals met with the Food and Drug Administration (FDA) in April 2013 and received an agreement that a New Drug Application (NDA) would be accepted for filing based on a single, strongly positive study (ACP-103-020) with supportive safety and efficacy data from earlier trials.

The pimavanserin NDA was submitted in September 2015 and was accepted with priority review in November 2015. The submittal included four placebo-controlled
studies in Parkinson’s Disease Psychosis subjects, including an initial 4-week proof of concept study (ACP-103-006; referred to as 006), and three 6-week controlled studies (ACP-103-012; ACP-103-14, ACP-103-020; referred to as 012, 014, 020, respectively). In addition, two open-label extension studies (ACP-103-010, ACP-103-015, referred to as 010, 015, respectively) were included. The 020 study was the pivotal study.

The Phase II proof of concept study 006 was published and did not demonstrate statistical significance. The 006 study was a multi-center randomized, placebo-controlled, double-blind trial of 4 weeks duration, with a 4-week follow-up period. Patients were randomly assigned to receive pimavanserin or placebo at a ratio of 1:1 after completing the screening and baseline evaluations. Fifteen sites enrolled patients; of which thirteen sites enrolled at least two patients and two sites enrolled only one patient. All sites were located within the United States. Patients received study drug daily for 4 weeks, starting with 20 mg (pimavanserin tartrate 20 mg = 17 mg pimavanserin) on day 1, with possible increases to 40 mg (34 mg pimavanserin) or 60 mg (51 mg pimavanserin) on days 8 and 15, respectively; depending on clinical response. Sixty patients were enrolled with moderate-to-severe PDP. This study was powered to detect effects (relative difference of five points) on motor symptoms through the Unified Parkinson’s Disease Rating Scale (UPDRS), Parts II (Activities in Daily Living) and III (Motor Examination).

Patients were evaluated at baseline (up to 14 days prior to study) and on study days 1, 8, 15, 28 and 57 (safety data only). The Scale for the Assessment of Positive Symptoms (SAPS), the Parkinson’s Psychosis Rating Scale (PPRS) and the Clinical Global Impression–Severity (CGI-S) were used to assess psychosis. Additional efficacy assessments include the UPDRS Part I (Mentation, Behavior and Mood), Part IV (Complication of Therapy) and Part VI (Activities of Daily Living) and Epworth Sleepiness Scale (ESS).

The SAPS domain scores for hallucinations and delusions and their combination was used in their analysis. The domain score for each individual section (hallucinations, delusions) were added together to yield a sum of SAPS hallucinations score (sum of all seven items – total score) and a sum of SAPS delusions score (sum of all thirteen items – total score). The SAPS total domain score was chosen as the principal efficacy outcome measure.

Sixty patients were enrolled into the study with 29 enrolled in the pimavanserin group and 31 into the placebo group. For the pimavanserin group, one patient withdrew before Day 28 due to an adverse event and 8 patients withdraw after Day 28 and before Day 57. For these 8 patients, one withdrew for an adverse event, one for protocol violation and 6 for other reasons. There were 20 completers in the pimavanserin arm. In the placebo group, three patients withdrew prior to Day 28. One patient had an adverse event, one had disease progression and the other one
withdrew for other reasons. Four patients withdrew after Day 28 and before Day 57. All four withdrew for other reasons. The placebo arm had 24 completers.

The mean final dose for pimavanserin was 44.8 ±16 mg. According to the SAPS, visual hallucinations followed by auditory was the most severe form of hallucinations at baseline. In comparing baseline to Day 28, there was a statistical significant improvement in the global rating of hallucinations in the pimavanserin group (p=0.02, effect size=0.58). The hallucinations domain score (total score) for the pimavanserin arm showed improvement, but it was not significant (p=0.16).

At baseline, persecutory delusions were the most frequent and severe forms of delusions, followed by delusions of jealousy. The pimavanserin group showed significantly greater improvement in the SAPS delusion measure for: persecutory delusions (p=0.009, effect size=0.41), ideas and delusions of reference (p=0.05, effect size=0.36), and global ratings of delusions (p=0.3, effect size=0.53). There was a trend for the SAPS delusion domain score to show improvement in the pimavanserin arm (p=0.6, effect size=0.56). When evaluating the total scores (hallucinations plus delusions), the global ratings total showed significantly greater improvement with pimavanserin (p=0.02, effect size=0.66). For the SAPS total domain score, there was a trend showing the pimavanserin group to show greater improvement (p=0.09, effect size=0.52).

For safety, there was no significant difference in the incidence of adverse events in the two study groups. Most common adverse effects reported with pimavanserin that occurred in ≥5% and more than placebo were: asthenia, peripheral edema, increase in blood urea nitrogen, balance disorder, freezing phenomenon and somnolence.

The 012 and 014 studies are currently not published, though the data from these studies are available via the FDA and meeting abstracts. Study 012 was a randomized, double-blind, placebo-controlled, fixed dose trial (N=298) investigating pimavanserin tartrate doses of 10 mg and 40 mg. Subjects were enrolled at 73 sites in the U.S., five European countries and India. The primary outcome measure was SAPS H+D (SAPS- hallucinations + delusions). Efficacy was not statistically different between placebo and pimavanserin arms (SAP H+D least-squares [LS] mean difference from baseline versus placebo for 10 mg [-0.07, 95% CI -1.7-1.59] and 40 mg [-1.16, 95% CI -2.83-0.51], which the investigators attributed to an enhanced placebo response. Study 014 was a double-blind, placebo controlled, fixed dose trial conducted in the U.S. and Europe. This trial was terminated early due to investigators decision that the study was unlikely to exhibit efficacy due to lack of significant improvement in the 012 study.

Study 020 was the pivotal study for gaining FDA approval for pimavanserin. Several design changes were made for this study based on previous failed
In reviewing studies 012 and 014, factors that positively correlated with effect size were identified and applied to the study design for the 020 study. The 020 study was completed only in the US and Canada, utilized centralized raters for evaluating the primary efficacy outcome in order to reduce inter-rater variability, exclusively used the 40 mg dose (pimavanserin tartrate 40 mg= pimavanserin 34 mg), reduced the frequency of visits and treatment arms, implemented a two-week lead-in period of psychosocial therapy to blunt the placebo response, and identified a different primary outcome [Scale for Assessment of Positive Symptoms – Parkinson Disease (SAPS-PD)]. Patients were enrolled into the study from August 11, 2010 and August 29, 2012. The SAPS-PD focuses on the SAPS subdomains for hallucinations and delusions. From these subdomains, the SAPS-PD uses five items out of the seven in the hallucinations subdomain and four items out of the thirteen items from the delusions subdomain. The authors concluded that the SAPS-PD retains reliability, sensitivity to change and effect size of the larger scale while improving specificity for PDP, reducing score variability and reducing administration time. Also, the authors believe that these characteristics support the use of SAPS-PD in clinical practice and clinical trials for PDP.

In Study 020, patients were randomized within each center in a double-blind manner in a 1:1 ratio with a block size of four. After screening, each patient entered a 2-week lead-in phase during which non-pharmacological brief psychosocial therapy adapted for Parkinson’s disease (BPST-PD) was used to identify placebo responders prior to baseline. Assessments were done at baseline and Days 15, 29, and 43. The primary outcome measure was the SAPS-PD that was completed by live video conference between the patient and a centralized, independent rater who was masked to treatment assignment. The secondary outcome measures included changes by day 43 in the Clinical Global Impression-Severity (CGI-S) and Improvement (CGI-I) scales completed by a site investigator who was masked to the SAPS-PD scores. The Unified Parkinson’s Disease Rating Scale Parts II and III (UPDRS II and III) were used. Exploratory measures included the Zarit-22 Caregiver Burden Scale (CBS) and scales for outcomes in Parkinson’s disease-sleep (Parts B and C) assessing night-time sleep quality (SCOPA-NS) and daytime wakefulness (SCOPA-DS).

This study screened 314 participants, allocated 199 patients to treatment and included 185 patients in the full analysis set. In the primary analysis, the pimavanserin group exhibited significant improvement compared to placebo in the SAPS-PD scores at Day 43 (-5.79 [37% improvement] vs. -2.73% [14% improvement], respectively, p=0.0006). The pimavanserin group showed significantly greater improvement in other measures of psychosis, including the full 20-item SAPS H+D score (pimavanserin [-6.51] vs. placebo [-3.14], p=0.0012); CGI-I (effect size 0.51, p=0.0011), and CGI-S (effect size 0.52, p=0.0007). The SAPS H+D showed a statistically significant decrease in this study. The SAPS H+D
was the primary outcome measure used in the previous trials, thus indicating that the positive results from the 020 study were not simply due to using the new SAPS-PD measurement as the primary outcome. The exploratory analysis showed significant improvement for pimavanserin vs. placebo in caregiver burden (effect size=0.50, p=0.0016), nighttime sleep (effect size=0.31, p=0.0446) and daytime wakefulness (effect size=0.39, p=0.0120) according to the Scales for Outcomes in Parkinson’s Disease-Sleep Scale (SCOPA-Sleep).

Studies 010 and 015 are extension studies. Study 010 enrolled 39 patients from Study 006. Study 010 was completed in May 2013. Study 015 was completed on May 30, 2018 (last day for assessment or intervention) and had an article published regarding the impact of current antipsychotic medication use on mortality and adverse events in patients with PDP. Study 015 enrolled patients from 012, 014 and 020. A total of 459 patients were enrolled in this multicenter, open-label extension of pimavanserin comparing patients taking and not taking current antipsychotics. The participants were divided into two groups: those receiving concomitant antipsychotic medications and those who did not take antipsychotic medications during the study. All participants were receiving pimavanserin 40 mg daily in addition to their medications for treating Parkinson disease. Safety assessments were completed at 2 weeks, 1, 3, 6, 9, and 12 months; and then every 6 months. There was a significant increase in mortality for those patients taking a concomitant antipsychotic medication compared to those that were not taking a concomitant antipsychotic medication (IRR 4.20, 95% CI 2.13-7.96). Patients who received concomitant antipsychotic medication as compared to those that didn’t were significantly more likely to experience overall a serious adverse event (IRR 2.95, 95% CI 2.02-4.24), any antipsychotic-related event (IRR 1.66, 95% CI 1.18-2.29), cognition-related events (IRR 2.70, 95% CI 1.19-5.58), infections (IRR 1.97, 95% CI 1.17-3.16), and edema (IRR 2.61, 95% CI 1.09-5.59). The risk of falls, stroke, sedation, orthostatic hypotension, and thromboembolic events was increased in the concomitant antipsychotic medication group, but it was not significant.

Other Indications

According to clinicaltrials.gov on June 11, 2019, the following were listed as trials with pimavanserin:

<table>
<thead>
<tr>
<th>Psychiatric Disease</th>
<th># of trials</th>
<th>Status</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s Psychosis</td>
<td>1</td>
<td>Completed</td>
<td>II</td>
</tr>
<tr>
<td>Psychiatric Disease</td>
<td># of trials</td>
<td>Status</td>
<td>Phase</td>
</tr>
<tr>
<td>--------------------------------------------------------------</td>
<td>-------------</td>
<td>-------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Alzheimer’s agitation &amp; aggression</td>
<td>1</td>
<td>Completed</td>
<td>II</td>
</tr>
<tr>
<td>Alzheimer’s agitation &amp; aggression</td>
<td>1</td>
<td>Terminated</td>
<td>II</td>
</tr>
<tr>
<td>Major Depression adjunctive</td>
<td>1</td>
<td>Completed</td>
<td>II</td>
</tr>
<tr>
<td>Parkinson’s &amp; Depression</td>
<td>1</td>
<td>Active, not recruiting</td>
<td>II</td>
</tr>
<tr>
<td>Parkinson’s &amp; impulse control</td>
<td>1</td>
<td>Not yet recruiting</td>
<td>II</td>
</tr>
<tr>
<td>Schizophrenia negative symptoms</td>
<td>1</td>
<td>Active, not recruiting</td>
<td>II</td>
</tr>
<tr>
<td>Schizophrenia – antipsychotic &amp; motor effects of pimavanserin administered in combination with haloperidol and risperidone</td>
<td>1</td>
<td>Completed</td>
<td>II</td>
</tr>
<tr>
<td>Neurodegenerative – neuropsychiatric symptoms</td>
<td>2</td>
<td>Recruiting</td>
<td>III</td>
</tr>
<tr>
<td>Schizophrenia – adjunct</td>
<td>1</td>
<td>Recruiting</td>
<td>III</td>
</tr>
<tr>
<td>Major Depression – adjunct</td>
<td>1</td>
<td>Recruiting</td>
<td>III</td>
</tr>
<tr>
<td>Schizophrenia – adjunct</td>
<td>1</td>
<td>Active, not recruiting</td>
<td>III</td>
</tr>
<tr>
<td>Dementia – related psychosis</td>
<td>1</td>
<td>Recruiting</td>
<td>III</td>
</tr>
</tbody>
</table>

Nasrallah, et al\textsuperscript{14} recently published a series of ten case reports involving patients with schizophrenia and schizoaffective disorder with refractory hallucinations and delusions who received a trial of pimavanserin when clozapine or multiple antipsychotics failed. According to the article, the addition of pimavanserin to
clozapine in patients with refractory hallucinations and delusions led to remission of the refractory psychotic symptoms after months of clozapine treatment. As a result, pimavanserin was tried as monotherapy in a few patients prior to using clozapine with the intent of reserving clozapine for those that failed pimavanserin monotherapy. In presenting these cases, the authors noted that this was not a research study, no rating scales were used to evaluate patient response and that the clinical improvement was determined by the treating psychiatrist and documentation as usual in the medical record. In addition, the article did not identify the number of patients that were treated and failed to respond to pimavanserin. Six patients had pimavanserin 34 mg added to clozapine and noted a response within 1 to 2 months with one case showing continued improvement through 5 months. In four cases, pimavanserin was used as monotherapy. The patients were noted to respond in 1 to 2 months, with one patient showing continued improvement over the next 8 months. The authors noted response in visual and auditory hallucinations (complete stoppage of hallucinations) and improvement in negative symptoms. Adverse effects were minimal and the pimavanserin seemed to be well tolerated. The case vignettes did not address response of pimavanserin on delusions. The authors suggest that double-blind, placebo-controlled trials of pimavanserin in refractory schizophrenia are warranted.

Meltzer, et al\textsuperscript{15} published their findings of a Phase II study that tested the hypothesis that augmentation of low doses of risperidone (2 mg/day) or haloperidol (2 mg/day) with pimavanserin (20 mg/day) can achieve efficacy comparable to risperidone 6 mg/day, but with lesser side effects. In this study, 423 patients were randomized to one of five treatment arms:

- risperidone 2 mg + placebo;
- risperidone 2 mg + pimavanserin 20 mg;
- risperidone 6 mg + placebo;
- haloperidol 2 mg + placebo; or
- haloperidol 2 mg + pimavanserin 20 mg

The primary efficacy measure was change in Positive and Negative Syndrome Scale (PANSS). The Barnes Akathisia Scale (BAS) and the Simpson-Angus Scale (SAS) were administered at baseline and 6 to 9 hours after the first dose and then at each study visit. The decrease in PANSS total score from baseline in the risperidone 6 mg + placebo, haloperidol 2 mg + pimavanserin and haloperidol 2 mg + placebo groups were not significantly different from each other or from the risperidone 2 mg + pimavanserin group at endpoint. The improvements from baseline to day 43 in the risperidone 2 mg + pimavanserin (-23.0), the risperidone 6 mg + placebo (-23.2), the haloperidol 2 mg + pimavanserin (-21.8) and haloperidol 2 mg + placebo (-25) groups were similar. There were no significant differences in motoric
tolerability (BAS, SAS) between the risperidone 2 mg + pimavanserin, risperidone 2 mg + placebo and risperidone 6 mg + placebo. The authors concluded that pimavanserin with a sub-effective risperidone dose (risperidone 2 mg + pimavanserin) was significantly more efficacious than the sub-effective dose of risperidone (2 mg + placebo) and produced fewer side effects than the standard risperidone dose (6 mg + placebo). Pimavanserin did not potentiate the haloperidol 2 mg dose but it did diminish the akathisia produced by haloperidol.

Ballard, et al\textsuperscript{16} published results of a Phase II study on the safety, tolerability and efficacy of pimavanserin in patients with Alzheimer’s disease psychosis. This was a randomized, double-blind, placebo-controlled single center with multiple affiliated nursing home sites across the UK. Patients were aged 50 years or older with possible or probably Alzheimer’s disease and psychotic symptoms including visual or auditory hallucinations, delusions or both. Patients were randomly assigned (1:1) to 12 weeks of oral treatment with either pimavanserin 34 mg/day or placebo. Pimavanserin showed efficacy in patients with Alzheimer’s disease psychosis at the primary endpoint (week 6) with acceptable tolerability profile and without negative effect on cognition. At 12 weeks, there was an absence of significant benefit of pimavanserin over placebo.

### Dosage Forms/Cost

<table>
<thead>
<tr>
<th>Name</th>
<th>Form</th>
<th>*Strength</th>
<th>AWP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pimavanserin tartrate</td>
<td>Tablet</td>
<td>10 mg</td>
<td>$3,646.80 (bottle of 30)</td>
</tr>
<tr>
<td>Pimavanserin tartrate</td>
<td>Capsule</td>
<td>34 mg</td>
<td>$3,646.80 (bottle of 30)</td>
</tr>
</tbody>
</table>

* Reflects actual pimavanserin strength

The 17 mg tablet has been discontinued.

### Special Considerations

**Boxed Warning\textsuperscript{3}**

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**

- **Pimavanserin is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson’s Disease Psychosis.**
Pimavanserin is distributed through specialty distributors, available through a limited number of group purchasing organizations and utilizes specialty pharmacy network for dispensing directly to patients. In October 2018, the agency’s current contracted wholesaler was added to the list of specialty distributors that can sell pimavanserin. To date, the agency’s current group purchasing organization does not have pimavanserin on contract. As a result, facilities pay approximately 83% of AWP.

For outpatient care, the prescriber either completes a Nuplazid™ treatment form or prescribes directly to a Nuplazid™ in-network specialty pharmacy and uses CoverMyMeds® (a healthcare software company that creates software to automate the prior authorization process used by some health insurance companies in the United States). The manufacturer provides support through the NUPLAZIDconnect™ program. This program provides patient access support, including navigating insurance, managing cost, and filling their prescriptions. The medication is delivered directly to the patient.

**Summary/Conclusion**

Pimavanserin is indicated for the treatment of hallucinations and delusions associated with Parkinson’s disease psychosis. In FY18, the State Hospitals identified 79 patients with Parkinson’s Disease out of 7,583 patients (1.04%). In completing a snapshot of individuals at the State Supported Living Centers, 20 individuals had Parkinson’s Disease on their active problem list out of 2,915 individuals (0.69%). PDP can develop in more than half the of the patients with Parkinson’s disease over the course of their illness. Thus, the number of patients/individuals affected by PDP is significantly small in the State Hospitals and State Supported Living Centers.

According to clinicaltrials.gov, there are several ongoing studies looking at the use of pimavanserin in schizophrenia, psychosis associated with neurodegenerative disease and major depression. These studies are either Phase II or III. A series of case reports recently published, suggests that pimavanserin might be useful in patients with schizophrenia or schizoaffective disorder with refractory hallucinations and negative symptoms. However, this report did not indicate the number of patients that were treated with pimavanserin nor were objective measures used to evaluate patients’ response. Similarly, the use of pimavanserin in treating Alzheimer’s Disease Psychosis is showing some promise. Currently, there is only enough evidence-based literature/studies to support the use of pimavanserin for Parkinson’s Disease Psychosis.
Recommendation

At this time, it is recommended not to add pimavanserin to the formulary due to the small number of patients/individuals potentially diagnosed with Parkinson’s Disease Psychosis. If needed for the treatment of this clinical state, pimavanserin can be obtained through the non-formulary process.

It is recommended that the literature be reviewed on a periodic basis for additional study findings regarding the use of pimavanserin in other disease states commonly treated within the organization.

References


Prepared by:
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State Hospital Pharmacy Advisor
**APPENDIX 1: NEW DRUG APPLICATION FORM**

Texas HHSC Health and Specialty Care System

NEW DRUG APPLICATION
(for inclusion in the State Operated Facilities Drug Formulary)

Date: __October 5, 2018__

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):

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**HHSC Psychiatric Executive Formulary Committee**

Information regarding new drug:

<table>
<thead>
<tr>
<th>Therapeutic Classification</th>
<th>Angiotensin II receptor blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic Name</td>
<td>losartan</td>
</tr>
<tr>
<td>Trade Name(s)</td>
<td>Cozaar®</td>
</tr>
<tr>
<td>Manufacturer(s)</td>
<td>Torrent, Macleods, Sandoz, Teva, West-Ward, Mylan, Watson, Lupin, Zydus, Aurobindo, Strides, Atembic, Upsher Smith, Apotex, Prinston, Micro Labs, IPCA, Cadista, Unichem, Hetero Labs, Hisun Pharm</td>
</tr>
<tr>
<td>Dosage Form(s)</td>
<td>tablet</td>
</tr>
</tbody>
</table>

Explain the pharmacological action or use of this drug antihypertensive

Explain the advantages of this drug over those listed in the formulary:
The system has high non-formulary use of losartan. All ARBs have had availability issues due to nitrosoamine contaminants that have been found in all products.

State which drugs this new drug would replace or supplement:
Olmesartan and valsartan. Both are on the reserve use list.

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

☐ 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

HHSC Psychiatric Executive Formulary Committee Minutes

August 2, 2019
Losartan potassium (Cozaar™)

Classification:
Nonpeptide angiotensin II receptor blocker (ARB)\(^1,2,3\)

**Pharmacology\(^1,2,3\)**
Losartan works through the Renin-angiotensin-aldosterone pathway (RAAS). It blocks the binding of angiotensin II, which is formed from angiotensin I via ACE enzyme and is a potent vasoconstrictor. Angiotensin II also stimulates the secretion of aldosterone by the adrenal cortex. Losartan and its active metabolite(s) inhibit the vasoconstrictor and aldosterone-secreting effects of angiotensin II selectively via AT1 receptor which is located in several tissues.

**Indications\(^1,2,3\)**
FDA-labeled indications include:
- Hypertension - adults and children > 6 years of age
- Diabetic nephropathy in T2DM with an elevated SCr and proteinuria (urinary albumin to creatinine ratio > 300 mg/g)
- Reduction of the risk of stroke in patients with hypertension and left ventricular hypertrophy

**Pharmacokinetics\(^1,2,3\)**

| Absorption       | Tmax: 1 hour  
|                  | Bioavailability: 33%  
|                  | Food effects: slows absorption; decreases Cmax, but only has minor effects on the AUC  
|                  | Carboxylic acid (active metabolite), Tmax, oral: 3-4 hours  
| Distribution     | Highly protein bound (98.7%) in human plasma.  
|                  | Volume of distribution (Vd): 34 L  
|                  | Carboxylic acid (active metabolite), protein binding: 99.8%  
|                  | Carboxylic acid (active metabolite) Vd: 12 L  
| Metabolism       | Hepatic: extensive first-pass metabolism via CYP2C9 and 3A4  
|                  | Carboxylic acid metabolite: active  
|                  | Substrate of CYP2C9; possible substrate of CYP3A4  

Excretion

- Renal clearance: 75 ml/min
- Renal excretion: 35% (4% unchanged, 6% as active metabolite)
- Fecal excretion: 60%
- Total body clearance: 600 ml/min
- Dialyzable: no (hemodialysis); no (peritoneal dialysis)

**Dosage/Administration**

**Adult hypertensive patients**

Dosing individualized; standard starting dose is 50 mg once daily, with 25 mg once daily dose used in those with possible depletion of intravascular volume (including patients treated with diuretics) and those with a history of liver impairment. Dosing range is 25-100 mg per day in 1 or 2 divided daily doses.

**Pediatric hypertensive patients > 6 years old**

Recommended starting dose is 0.7 mg/kg once daily (up to 50 mg total) given as a tablet or a suspension. Dose adjustments made according to patient blood pressure response. Doses over 1.4 mg/kg/day (or above 100 mg/day) have not been studied in pediatric patients.

**Diabetic nephropathy in T2DM**

Dosing individualized; standard starting dose is 50 mg once daily. The dose should be increased to 100 mg once daily based on patient blood pressure response.

**Reduction of the risk of stroke in patients with hypertension and left ventricular hypertrophy**

Recommended starting dose is 50 mg once daily. May increase to 100 mg once daily based on patient blood pressure response. May use in combination with a thiazide diuretic.

**Use in Special Population**

**Adults**
- Renal impairment: no adjustment needed
- Renal impairment, volume depleted patients: start at 25 mg once daily; adjust according to blood pressure response; a 25 mg dose given BID may be needed
- Liver impairment (mild-moderate): start at 25 mg once daily
- Hemodialysis: no adjustment needed

**Pediatric**
- Renal impairment (eGFR < 30 ml/min): use not recommended

**Pregnancy**
Drugs that act directly on the renin-angiotensin system can cause injury or death to the developing fetus. Discontinue as soon as possible if pregnancy is suspected. Pregnancy category D.

Lactation
Significant levels of losartan and its active metabolite were shown to be present in rat milk, however there are no studies showing whether losartan is excreted in human milk. Therefore, a decision should be made whether to discontinue nursing or discontinue the medication since there is a potential for adverse effects to the nursing infant.

Contraindication\textsuperscript{1,2,3}
Losartan is contraindicated in those who are hypersensitive to any component of this agent.

Allergic cross-reactivity for ARBs is not well-established, however the possibility cannot be ruled out due to similarities in chemical structure and/or pharmacologic actions.

Do not take losartan along with aliskiren in patients with diabetes. Losartan decreases the effects of aliskiren.

Precautions\textsuperscript{2}
Losartan Potassium can cause hypotension, that is sometimes symptomatic, in volume-depleted or salt-depleted patients which can include those being treated with diuretic therapy.

Avoid use of losartan with other renin-angiotensin system inhibitors.

Hyperkalemia has also been reported with use of losartan. Concomitant use with other drugs that may increase serum potassium may lead to the hyperkalemia. Monitoring is recommended. Dose reduction or interruption may also be necessary if hyperkalemia occurs.

Renal function deterioration, including acute renal failure, may occur. There is an increased risk with chronic kidney disease, renal artery stenosis, severe congestive heart failure, or volume depletion. Withholding or discontinuation of losartan may be necessary.

Adverse Effects\textsuperscript{3}
In controlled clinical trials, discontinuation due to adverse events occurred in 2.3% of patients receiving losartan compared to 3.7% of patients receiving placebo.

In 4 clinical trials of losartan for hypertension involving over 1000 patients, the adverse events that occurred in \geq 2\% of patients treated with losartan and more
commonly than placebo were: dizziness (3% vs. 2%), upper respiratory infection (8% vs. 7%), nasal congestion (2% vs. 1%), and back pain (2% vs. 1%).

Less common adverse events reported include: anemia, depression, somnolence, headache, sleep disorders, paresthesia, migraine, vertigo, tinnitus, palpitation, syncope, atrial fibrillation, CVA, dyspnea, abdominal pain, constipation, nausea, vomiting, urticaria, pruritis, rash, photosensitivity, myalgia, arthralgia, impotence, and edema.

During post-marketing the following side effects were reported: Hepatitis, malaise, thrombocytopenia, angioedema, hypersensitivity, hyperkalemia, hyponatremia, rhabdomyolysis, dysgeusia, dry cough, and erythoderma.

Persistent cough associated with ACE-inhibitor use is often a cause for discontinuation. Two studies of hypertension patients who experienced cough while receiving an ACE-inhibitor were randomized to losartan, lisinopril, placebo, or hydrochlorothiazide. The authors found that, in a population that had cough associated with ACE-inhibitor therapy, the incidence of cough with losartan is similar to hydrochlorothiazide or placebo.

**Monitoring**

Evaluate blood pressure response until control is achieved in patients initiating or adjusting antihypertensive medication.

Monitor renal function periodically in patients whose kidney function may depend on the activity of the renin-angiotensin system (e.g., renal artery stenosis, chronic kidney disease, severe congestive heart failure, volume depletion) or in patients receiving concomitant NSAIDs.

Monitor serum potassium periodically during treatment, especially when used concomitantly with drugs that may raise potassium levels.

Monitor electrolytes in patients receiving concomitant agents that affect the renin-angiotensin system.

In patients initiating antihypertensive therapy, monitoring the following at baseline and as clinically indicated: fasting blood glucose, serum creatinine, electrolytes, urinalysis, lipid profile, and CBC.

Electrolytes and renal function should be assessed 2-4 weeks after initiating losartan. Serum sodium and potassium should be monitored during dose titration.
Interactions$^{1,2,3}$

Losartan has the following clinically important drug interactions:

**Aliskiren**
- Concomitant use of aliskiren with losartan is contraindicated.

**Agents increasing serum potassium**
- Coadministration of losartan with other drugs that may raise serum potassium levels may result in hyperkalemia

**ACE-inhibitors**
- Concomitant use of an ACE-inhibitor along with losartan is not recommended.
- Dual blockade of RAAS system increases risk of hypotension, hyperkalemia, and renal impairment. Either can increase toxicity of the other and should not be used together.

**Cimetidine**
- Administration of losartan in conjunction with cimetidine led to a 18% increase in AUC of losartan, but it did not affect the PK of its active metabolite.

**Phenobarbital**
- Administration of losartan in conjunction with phenobarbital led to a 20% reduction in the AUC of losartan and its active metabolite.

**Rifampin**
- Administration of losartan in conjunction with rifampin led to an AUC reduction [40% AUC reduction in the active metabolite; 30% AUC reduction in losartan].

**Fluconazole**
- Administration of losartan in conjunction with fluconazole decreased the AUC of the active metabolite by 40%, but it increased the AUC of losartan by 70% following multiple doses.

**Lithium**
- Lithium excretion may be reduced if coadministered with losartan.
- Serum lithium levels should be monitored closely if lithium salts are to be co-administered with ARBs.

**NSAIDs (including COX-2 inhibitors)**
• In those who are elderly, volume depleted (on diuretic therapy), or with poor renal function, use of losartan with NSAIDs may result in deterioration of kidney function, including possible acute renal failure. These effects are usually reversible.

**Efficacy**

Four studies of losartan as monotherapy were completed to study the efficacy for hypertension. In these studies, 1075 patients were randomized to several doses of losartan and 334 to placebo. Doses of 50, 100, and 150 mg once daily gave statistically significant systolic and diastolic mean decreases in blood pressure compared to placebo. The dose of 150mg did not have a greater effect than the 50 or 100mg doses. A larger trough was found in response to twice daily doses of 50 and 100mg doses compared to the once daily dosing. Men, women, patients under 65, and patients over 65 had similar responses. Losartan was effective in blood pressure reduction regardless of race, but the effect was less in African American patients (usually a low-renin population).³

The 2017 ACC/AHA Hypertension guidelines recommend thiazide diuretics, calcium-channel blockers (CCBs), ACE inhibitors, or ARBs as first line therapy. Patient factors such as race and comorbid conditions should be considered when choosing a specific class. For African American patients, ARBs may be better tolerated than ACE inhibitors, with less cough and angioedema, but there is currently no proven advantage over ACE inhibitors in preventing stroke or CVD in this population. These guidelines also recommend that patients with chronic cough, a history of ACE inhibitor-induced cough, or bronchial responsiveness while on an ACE inhibitor should use an ARB instead.⁴

The LIFE study compared losartan and atenolol in hypertensive patients with ECG-documented left ventricular hypertrophy. Patients received losartan 50 mg or atenolol 50 mg. If goal blood pressure was not met, hydrochlorothiazide was added first, followed by an increase in dose of losartan or atenolol to 100 mg. Other antihypertensives were added for blood pressure control after these initial steps if needed. The primary endpoint was first occurrence of cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction. Treatment with losartan resulted in a 13% reduction in risk of primary endpoint compared to the atenolol group. Treatment with losartan reduced the risk of stroke by 25% relative to atenolol.³

In the RENAAL study, patients with type 2 diabetes with nephropathy were randomized to losartan 50 mg once daily or placebo. The drug was titrated to 100 mg if blood pressure was not achieved. The primary endpoint was the time to first occurrence of any of the following events: doubling of serum creatinine, end-stage renal disease, or death. Treatment with losartan resulted in a 16% risk reduction in this primary composite endpoint.³
## Dosage Forms/Cost

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Price/tablet</th>
<th>Price/month (30 tablets)</th>
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<tbody>
<tr>
<td>Losartan</td>
<td>25 mg</td>
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<tr>
<td>Losartan</td>
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<tr>
<td>Lisinopril</td>
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<tr>
<td>Lisinopril</td>
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</tr>
</tbody>
</table>

## Special Considerations

**Boxed Warning\(^2\)**

- Discontinue losartan as soon as possible when pregnancy is detected.
  Fetal injury or death can be caused by drugs that act directly on the renin angiotensin system.

## Summary/Conclusion

Losartan is FDA approved for hypertension, diabetic nephropathy in type 2 diabetes mellitus with an elevated SCr and proteinuria, and reduction of the risk of stroke in patients with hypertension and left ventricular hypertrophy. It has been studied in many different trials, has a favorable side effect profile, and is a first-line therapy option for hypertension. In addition, it is available as a generic and is comparable in cost to the example ACE-inhibitor, lisinopril.

## Recommendation

It is recommended to add losartan to the drug formulary on regular status due to its efficacy for a number of indications and its place in the hypertension guidelines. Generic losartan is also comparable in cost to the example ACE-inhibitor, lisinopril. Manufacturers are currently producing impurity-free losartan, however, due to past
recalls, it is recommended that literature and FDA updates be monitored on a periodic basis for additional recall status information.

References


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