HHSC Psychiatric Executive Formulary Committee Minutes

The HHSC Psychiatric Executive Formulary Committee (PEFC) convened on January 27, 2023 via MS Teams. The meeting was called to order by Dr. Moron as Chair, at 9:30 a.m.

Members

Member Names	Attendance	Member Names	Attendance
Yekini Adeyemi, RN	Absent	David Moron, MD- Chair	Present
Angela Babin, RPh	Present	Leah Nunez, PharmD	Present
John Bennett, MD	Present	Brittany Parmentier, PharmD	Present
Giovanna Betancourt, PharmD	Present	Kasey L. Pena, PharmD- Secretary	Present
Rakesh Chadalavada, MD	Present	Kenda Pittman, PharmD	Present
German Corso, MD	Present	Sangeetha Rajan, MD	Present
Brad Fitzwater, MD	Present	Rishi Sawhney, MD	Present
Jon Guidry, MD	Present	Lesia Trickett, MD	Present
Catherine Hall, PharmD	Present	Ashton Wickramasinghe, MD	Present
Dana Hopkins, RN	Absent	Patrick Young, MD	Absent
Jeffery Matthews, MD	Present		

Guests Present: Tonya Barrios, State Hospitals Central Administration; John Fullerton, PharmD, Lufkin State Supported Living Center; Kristen Neumeister, PharmD, North Texas State Hospital; Nicole Freeman, PharmD, Corpus Christie State Supported Living Center; Bethany Whitaker, PharmD, Austin State Supported Living Center; Nhi Nguyen, P4 PharmD Student, University of Houston

Opening

Introduction and Other Information

Kasey Pena, PharmD, introduced Dr. Guidry, North Texas State Hospital- Vernon, who has replaced Dr. Shero as a state hospital physician member of this committee.

Annual Conflict of Interest Disclosures

A signed disclosure form has been received from each committee member. The committee reviewed one disclosed potential conflict made by a member that was on the speakers' bureau for a formulary product. The committee agreed that the member will refrain from participating in discussions or voting on any actions regarding that medication.

Review of Minutes

The minutes from the October 28, 2022 meeting were approved as previously distributed.

Unfinished Business

None

New Business

New Drug Applications

meropenem (Merrem®)

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

After discussion of the monograph, the committee approved the addition of meropenem (Merrem) to the formulary as a Reserve Drug in the Infectious Disease Agents- Miscellaneous Antibiotics section.

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

pimavanserin (Nuplazid®)

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

After discussion of the monograph, the committee recommended to decline to add pimavanserin (Nuplazid) to the formulary at this time. The committee recommended that the literature be reviewed in two years for additional data on the safety and efficacy of pimavanserin.

Psychotropic Medication Audit Criteria & Guidelines Review

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

- bupropion
- esketamine
- mirtazapine
- MAOIs
- nefazodone/trazodone

The updated documents will be posted to the PEFC website.

Psychotropic Monitoring Guidelines Review

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

Adverse Drug Reaction Reports

The committee discussed five adverse drug reaction reports that were received from the field. These adverse events were reported to the FDA's MedWatch program.

ADR: clozapine/myocarditis

A 22-year-old white male with a history of schizophrenia, autism spectrum disorder, and tinea pedis admitted to the psychiatric hospital mid-September. No known history of allergies or exposure to clozapine and identical twin prescribed and tolerating clozapine well. On admission client prescribed Depakote ER 1500 mg PO daily, clonidine 0.1 mg PO twice daily, Invega Sustenna 234 mg IM every 21 days and chlorpromazine 800 mg PO daily. Admission labs including CBC and CMP were wnl. Valproate level 79.3 mcg/mL. EKG with QTC 433ms, normal sinus rhythm. During his admission, his pulse prior to clozapine initiation ranged daily from 80 BPM-125 BPM. Divalproex ER was titrated to 1750 mg at bedtime; supratherapeutic VPA level of 126.3 mcg/ml (9:26 am) a week later, however peak not trough. CBC and CMP wnl. Due to medication refusal, clonidine was tapered. The chlorpromazine dose was also tapered due to daytime sedation and in preparation for clozapine initiation and discontinued one week after initiation of clozapine.

Clozapine was started mid-October after baseline CBC, CRP (range <0.5mg/dL): <0.3 mg/dL and Troponin T (range <22 ng/L): 9 ng/L wnl.
Clozapine was titrated as follows:
Day 1 Clozapine 25mg/day was initiated, pulse 100BPM
Day 3 Increase to 50mg/day, pulse 105BPM
Day 4 Increase to 100mg/day, pulse 99BPM
Day 6 Increase to 150mg/day, refused vitals
Day 7 CBC wnl. C Reactive Protein (range <0.5mg/dL): <0.3 mg/dL, Troponin T (range <22 ng/L): 7 ng/L; EKG QTC 415ms, normal sinus rhythm
Day 8 Increase to 200mg/day, refused vitals
Day 10 Increase to 250mg/day, pulse 99BPM
Day 12 Increase to 300mg/day, pulse 102BPM
Day 14 Clozapine morning dose (100mg) given, C Reactive Protein (range <0.5mg/dL): 2.3 mg/dL and Troponin I (range <0.1ng/mL): 0.61ng/mL both high; CBC wnl except WBC (range 3.5-10.0 K/mm3): 10.6 K/mm3, Absolute monocytes (0.10-1.00 K/mm3): 1.33 K/mm3, pulse 117BPM, noted to be tired and complaints of wanting to sleep, clozapine was discontinued after morning dose on Day 14 due to elevated troponins and "slight" tachycardia, but he was otherwise noted as being asymptomatic at that time.

The following day Troponin T (range <22 ng/L): 123 ng/L, EKG QTC 436ms, sinus tachycardia, pulse 116BPM/ 120BPM (repeat).

Client was transferred to a local medical hospital for further evaluation of possible myocarditis due to clozapine. Medical hospital labs: Troponin I: 0.26 HIGH, BNP: 163 HIGH. Next medical hospital day Troponin I: 0.15 HIGH, (repeat) 0.11 HIGH, (repeat) 0.06 HIGH. Third hospital day transthoracic ECHO was within normal limits, troponins had normalized, and vitals were stable and returned to the psychiatric hospital. Throughout this time the client remained asymptomatic (lacked chest pain, shortness of breath, edema, flu-like symptoms including fever), even during times of high troponin levels. Clozapine rechallenge with 12.5 mg starting dose and 12.5 mg weekly titration started 2 weeks after initial discontinuation of clozapine and 10 days after troponins normalized without recurrence as of day 8 after restarting clozapine.

Pharmacist Impressions:

Patient had a 14-day trial with clozapine that was discontinued due to suspected medication-induced myocarditis. The estimated absolute risk of clozapine-induced myocarditis and cardiomyopathy is 0.01% to 0.19% with most cases occurring between 14-30 days after initiation (*Journal of Clinical Psychopharmacology, 41* (2), 180-185). Clozapine-induced myocarditis does not appear to be dose related; case studies show incidence with doses ranging between 50 mg – 600 mg per day. It's important to acknowledge that myocarditis may begin as being asymptomatic or having non-specific symptoms such as fever or tachycardia, but ultimately can be fatal. Although clozapine-induced myocarditis does not have a clear mechanism, elevated CRP, monocytosis and eosinophilia have been observed as markers in addition to abnormal troponins and EKG. This client had elevated troponins, CRP, monocytes and tachycardia noted on EKG. Other than some general lethargy which could have been related to the sedating effects of the medication itself, there were no other reported symptoms of myocarditis noted including chest pain, shortness of breath, edema, or flu-like symptoms including fever.

Valproate use while initiating clozapine has been associated with an increased risk for myocarditis with one study finding a nearly 2.5-fold risk with concomitant use (Schizophrenia research. 2012 Nov 1;141(2-3):173-8). The proposed mechanism involves valproate acting as a catalyst for inflammatory processes via antagonism of peroxisome proliferator-activated-receptor-gamma (PPAR-γ). PPAR-γ antagonism increases circulating monocyte activation, which can lead to increased risk of a hypersensitivity reaction to the clozapine-myocyte antigen complex. Additionally, the patient's valproate level was high on 10/6/22 at 126; although, peak rather than trough level was obtained.

Based on the information available this appears to be possible clozapine-induced myocarditis which was caught early due to routine laboratory surveillance resulting in favorable outcome with unremarkable transthoracic ECHO.

ADR: clindamycin/seizure

A 30-year-old white male who bangs his head frequently as an expression of frustration (SIB) had a "hard" 2-minute seizure on 05/04/2022 from 18:36 to 18:38. The initial report by the campus RN was that he did not have a history of seizures, but this is not the case; his last seizure was on 9/24/2021. He is maintained on oxcarbazepine for them and followed by Neurology. He was post-ictal for 7 minutes and then was back at his baseline, and the description of the seizure activity was consistent with his history of focal seizures. He did receive a non-contrast CT of his brain which showed no acute abnormalities by verbal report. We have requested and are still awaiting the results of other tests which were done. He returned with a prescription for levetiracetam 500 mg twice daily for 14 days, having received a loading dose of 1000 mg in the ER, but we are going to take alternative actions to address this as will be discussed.

Recent history is notable for an elevated blood pressure reading of 146/92 at 13:30 on 4/26. No HA or other associated symptoms were noted. On 5/2 at 05:40 he complained of dysuria (which he later denied), an episode of urinary incontinence, and urinating small amounts with hesitation. A UA with culture if indicated was collected with results positive for nitrites with large leukocyte esterase, >100 WBCs/HPF, 10-25 RBCs/HPF, and many bacteria. Culture and sensitivity results have not arrived yet. On 5/2 at 06:30, he banged his head very hard and caused a good-sized hematoma and was started on moderate neuro checks. The following afternoon at 13:19 notified that his right wrist, which he also bites repeatedly when agitated, had developed pustules despite being on a topical antibiotic ointment. Because this has been an ongoing issue with delayed healing, a consult be sent to Hab Therapy was requested to see if we could come up with some protection for that wrist as well as to supervise healing. A culture of the wound was obtained and shows moderate gram-negative rods and a small amount of gram-positive cocci. He was prescribed a 7-day course of clindamycin 300mg three times daily and received his first dose at 19:00 on 5/3. At 30 min after midnight on 5/4 he head banged again, and at 01:42 he bit a peer; later that afternoon his LOS was increased due to these acts of SIB and aggression. Medications prescribed at time of event include atorvastatin, brexipiprazole, lorazepam, montelukast, oxcarbazepine, sertraline, and tamsulosin.

ADR: oxaliplatin, irinotecan/rash

A 53-year-old Hispanic female receiving chemotherapy at the Oncology office had a drug reaction halfway through oxaliplatin and irinotecan infusion. The reaction consisted of a red rash to various parts of her body. She was reported not to have an anaphylactic reaction with anasarca, SOB, rhinorrhea, or LOC. Patient received methylprednisolone, a nebulizer treatment, and diphenhydramine 25 mg while at the office and had orders to receive diphenhydramine 25 mg and prednisone 10 mg last night, per Oncology. Nurse denied any other sequela upon her return to the dorm.

Medications prescribed at time of event include lamotrigine, megestrol, and esomeprazole.

ADR: clozapine/bowel obstruction

A 41-year-old white male with profound intellectual developmental disability, autistic spectrum disorder, constipation, seizure disorder, hiatal hernia found on CT 5/4/21, GERD diagnosed 2021, and non-goblet metaplasia identified during EGD 7/2021. Medications prescribed at time of event include clozapine, clonidine, clobazam, levetiracetam, lacosamide, pantoprazole, bisacodyl, and polyethylene glycol. Clozapine dose adjustment history includes the following 575 mg daily (1/18/19), 625 mg daily (3/2/19), 650 mg (1/22/20), 675 mg (3/19/20), 650 mg (7/21/21). Clozapine/nor-clozapine serum level history includes the following 267/120 ng/mL (10/18/19) 297/158 ng/mL (2/3/20), 404/165 ng/mL (4/6/22), 360/162 ng/mL (12/24/21).

Patient was sent to the ER on 8/9/22 following emesis and abdominal distension. He was admitted for partial/early small bowel obstruction per CT abdomen and pelvis. He was NPO during the first day of hospitalization then all medications were restarted except his bowel regimen due to loose stools. The clozapine was discontinued upon discharge on 8/12/22 due to guardian request with the plan for psychiatry to evaluate risk versus benefit. He was then readmitted to the hospital on 8/13/22 following emesis. During this second extended hospital stay, it was determined that clozapine should not be restarted due to potential risks and the possible contribution to the initial small bowel obstruction (SBO). On 8/19/22 the KUB showed involvement of the whole colon, patient was started on TPN and GI consulted for possible surgery. Pyridostigmine was started at 20 mg twice daily then later reduced to 12 mg twice daily to promote bowel motility and reduce the risk of future occurrence. The obstruction resolved with bowel rest and ultimately did not require surgical intervention. Patient was gradually restarted on PO medications and nutrition, and he has returned to his baseline.

Patient has been on clozapine since 2010 and has had two documented small bowel obstructions during that time. The first was in May 2021 when he had a viral gastroenteritis resulting in adynamic ileus and early/incomplete bowel obstruction, and the second was the current event noted here of a partial SBO. The current SBO was evaluated by GI and a general surgeon at the hospital who noted no identified etiology. Cases of bowel obstruction and paralytic ileus have been reported with clozapine use that have occasionally resulted in hospitalization or death; in 2020 the FDA strengthened its warning of these side effects. The risk worsens with higher doses and serum levels. Of note, prior to reaching a clozapine dose of 675 mg daily, his combined serum clozapine plus nor-clozapine levels were mostly <500 ng/ml with a few outliers; this higher serum level appears to correlate with the patient's increased frequency of significant adverse events.

ADR: denosumab/osteonecrosis

A 58-year-old white female with profound intellectual disability secondary to neonatal pneumococcal meningitis at two days of age, cerebral palsy with spastic quadriplegia, generalized tonic-clonic seizure disorder, C4-5 fracture on 2/20/22 s/p posterior fusion 2/21/22, GERD, constipation, osteopenia, and history of drug allergy to cefepime/piperacillin-tazobactam (rash 2021). Medication orders at time of event include denosumab, esomeprazole, lamotrigine, levetiracetam, midodrine, polyethylene glycol, calcium, cholecalciferol, ascorbic acid, ferrous sulfate, docusate sodium, and cetirizine.

The patient started Reclast (zoledronic acid) in 2011, this was changed to Prolia (denosumab) from 2012-2015 then back to Reclast starting 11/17/15. Her DEXA was completed on 4/13/22 and noted a decrease in bone mineral density (BMD) by 8.7%, also of note, she sustained a closed fracture of the fourth cervical vertebra on 2/20/22. Following these events, Reclast was changed to Prolia on 4/14/22 with the goal of improved BMD with an alternative mechanism of action; she received one dose on 4/14/22 then it was discontinued on 10/12/22 prior to any subsequent doses.

The patient had a dental cleaning on 6/15/22 in which the upper right palate area was evaluated and no concerns were identified. Then during her dental cleaning on 8/25/22, an area of exposed bone lingual to #2 area in the tuberosity/palatal region <0.5 in size as well as a bony prominence in #15 area were noted, and she was referred to an oral surgeon. She was seen by an oral surgeon on 10/12/22 and it was suspected that she may have bisphosphonate related (later clarified as "drug-related") osteonecrosis of the jaw, stage I-II. A CT was requested to confirm. The CT was completed on 10/14/22 and did not show evidence of osteonecrosis, however the oral surgeon reviewed the CT and noted that the "exposed bone is itself suggestive of osteonecrosis stage 1" and he strongly suggests we go with the diagnosis of drug induced osteonecrosis. Surgical interventions are not recommended at this time, and there is no identified infection that needed to be addressed. Chlorhexidine mouthwash used for suction toothbrush cleaning was increased from daily to twice daily on 10/13/22 as a preventative measure.

Per the package insert, studies have shown that denosumab resulted in osteonecrosis of the jaw in up to 6.6% of patients. It appears that the timing of the patient's diagnosis occurred after restarting denosumab in 2022; of note, she did receive denosumab in 2013-2015 with no concerns noted during that time period. She also received multiple doses of zoledronic acid, therefore it is difficult to confirm that denosumab and not zoledronic acid is the cause. Risk factors of ONJ include facial fracture or trauma; while she did not have a facial fracture, she did experience a cervical fracture in February 2022 which resulted in a cervical fusion procedure.

Given the timeline of events, the long-term use of osteoporosis treatment which included a bisphosphonate and a RANKL inhibitor, and the known risk of this drug reaction associated with osteoporosis agents, it is likely that one of these agents was

the cause of this adverse drug reaction. Denosumab was recently started and was administered 6 months prior to the identification of OJN making it the likely causative agent but zoledronic acid cannot be fully ruled out due to the long half-life.

HHSC Psychotropic Medications Consent List Annual Review

The committee reviewed and approved the following changes to the list of psychotropic medications requiring consent:

- Remove maprotiline (Ludiomil)
- Add "Reserve" to the paliperidone palmitate LAI (Invega Trinza) listing
- Add amantadine (Gocovri) to Miscellaneous Drugs
- Remove "nonformulary" from clonidine ER (Kapvay) listing
- Remove "Other: This category must be approved prior to inclusion in this Instrument" section

The committee also discussed the removal of discontinued brand name medications and decided since this is a resource document used by many the brand names should remain.

The updated document will be posted on the PEFC website.

Antipsychotic Tier Schedule Annual Review

The committee reviewed and approved recommended revisions to the Antipsychotic Tier Schedule:

- Add paliperidone palmitate LAI (Invega Trinza) as a Tier 2
- Remove quetiapine ER
- Updated reference
- Updated Cost Index of several items

Additionally, the committee discussed the recently discontinued Sunovion PAP program for Latuda, which will have significant cost impacts to the LMHA's. Latuda is high in cost and the LMHA's may struggle with continuing the medication in the community once a patient is discharged from inpatient locations. The generic is set to come out in February 2023, but the cost is not likely to be significantly reduced compared to brand. The group decided to disseminate the information shared to their respective facilities to inform prescribing.

The updated 2023 HHSC Antipsychotic Tier Schedule will be posted on the PEFC website.

Drug Formulary Sectional Review

In reviewing the formulary drug listings for Blood Modifying, Antidotes, Substance Use Treatments, Antidiabetic, Parenteral Solutions and Additives, the following changes were approved:

- Blood Modifying Agents-Antiplatelet Agents
  - aspirin – remove caplet, oral
- Substance Use Treatments
  - buprenorphine – remove brand name Subutex
  - disulfiram – remove brand name Antabuse
  - nicotine:
    - ◊ remove brand name Nicotrol
    - ◊ add lozenge, oral
- Antidiabetic Agents-Miscellaneous Antidiabetic Agents
  - repaglinide – remove brand name Prandin
- Updated Cost Index of several items

The updated formulary will be posted on the PEFC website.

Other Formulary Changes

The committee also approved the following changes to the formulary:

- Reserve table: Updated buprenorphine, buprenorphine-naloxone (Suboxone) Guidelines for Use language to match updated regulations for prescribing buprenorphine.

The updated formulary will be posted on the PEFC website.

Quarterly Non-Formulary Drug Justification Report

For the first quarter of fiscal year 2023 (September 2022 to November 2022), only the state hospitals reported use of non-formulary agents. The state supported living centers (SSLCs) currently do not have the capability to obtain non-formulary drug usage reports from their computer system but are working with the vendor to make this reporting possible. The following were the top six non-formulary agents, by number of orders, that were prescribed in the state hospitals during the first quarter of fiscal year 2023:

- NAC (acetylcysteine)
- Paxlovid
- Molnupiravir
- Midol Menstrual Complete
- Listerine Zero
- Magnesium oxide

Issues from the Chief Medical Officer, State Hospitals

Dr. Matthews had no issues to report.

Issues from the Medical Services Coordinator, SSLCs

Dr. Wickramasinghe shared with the committee a useful phone app, PneumoRecs VaxAdvisor, created by the CDC, which is a helpful new tool to keep track of the complicated schedules of pneumococcal vaccines.

Dr. Wickramasinghe also announced he will be conducting scheduled luncheons with CME on aspiration pneumonia.

Drug Shortages, Recalls, and FDA Safety Communications

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

Shortages

- Lithium oral solution: unavailable, shortage of an active ingredient (since 2020). Capsules still available.
- Neomycin tablet: unavailable. Topical still available.
- Oxybutynin syrup: unavailable. Tablets still available.

The following medications are in shortage but are still available to be ordered on allocation (1/20/2023):

- Amphetamine salt combos
- Amoxicillin oral powder for suspension (NEW)
- Furosemide vial for injection (NEW)
- Lorazepam injection
- Methylprednisolone acetate injection
- Sterile water for injection
- Sucralfate tablets (NEW)
- Rifampin
- Epinephrine Auto-Injector
- Ozempic (semaglutide)

Recalls

- Vancomycin injection (Hospira brand): recalled due to presence of visible glass particulates (12/27/2022)
- Magnesium Citrate Oral Solution: Worldwide recall of some brands of mag citrate due to potential gluconacetobacter liquefaciens contamination. Not available to ordered. (8/2022)
- Milk of Magnesia: Nationwide recall of Major brand magnesium hydroxide/aluminum hydroxide/simethicone oral suspension due to microbial contamination. Still available to be ordered. (8/2022)

Safety-related Labeling Changes

- Aripiprazole (Abilify): FDA added "blood prolactin decreased" as a frequent adverse reaction observed in clinical trials.
- Amoxicillin (Amoxil): FDA added a section detailing the risk of Severe Cutaneous Adverse Reactions, included rashes, SJS, TEN, DRESS, etc. Patients should be advised about the possible signs and symptoms of serious skin adverse effects and instructed to stop taking immediately at the first sign of skin issues.
- Lorazepam injection (Ativan): Additional information regarding the risk of using lorazepam in pregnancy. The use of injectable lorazepam late in pregnancy can result in sedation and/or withdrawal symptoms in newborns. Patients should be advised about a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to the lorazepam injection during pregnancy.
- Topiramate (Eprontia): Information added warning of the risk of decreased mineral bone density and negative effects on growth and increase in urinary calcium in pediatric patients. These risks were identified by a controlled trial that indicated that pediatric patients treated with topiramate demonstrated decreased lumbar spine bone mineral density correlated with decreased serum bicarbonate (likely caused by metabolic acidosis). This study also showed an increase in urinary calcium and decrease in urinary citrate; this increased ratio increases the risk of kidney stones.
- Voriconazole (VFEND): FDA added further information related to possible skin related reactions

News Briefs

The following information was shared with the committee members:

FDA Approves Second Anti-Amyloid for Alzheimer's Disease

Medscape (1/6/2023) reports that the FDA has approved lecanemab (Leqembi, Eisai) for the treatment of early Alzheimer's disease based on the CLARITY AD trial. After 18 months of treatment, lecanemab slowed cognitive decline by 27% compared with placebo (measuring using the Clinical Dementai Rating-Sum of Boxes). There are some adverse events associated with this medication, including amyloid related imaging abnormalities that manifest as edema or microhemorrhages. These occurred in 1 in 5 patients taking lecanemab. The other anti-amyloid medication for Alzheimer's Disease is adacunumab (Aduhelm, Biogen/Eisai). The Alzheimer's Association has filed a formal request with CMS to ask that it provide full and unrestricted coverage for FDA approved AD treatment.

CDC and FDA Identify Preliminary COVID-19 Vaccine Safety Signal for Persons Aged 65 Years and Older

US FDA (1/13/2023) reports that one of the safety monitoring systems used to detect possible safety signals for vaccines, the CDC Vaccine Safety Datalink (VSD)

triggered additional investigation into whether there was a safety concern for ischemic stroke in people ages 65 and older who received the Pfizer-BioNTech COVID-19 Bivalent Vaccine. Per review of the data, it appeared there was an increased likelihood of having an ischemic stroke in the 21 days following vaccination compared to days 22-44 days post vaccination. Other safety monitoring systems (CDC Vaccine Adverse Event Reporting System, for example) have not flagged a similar concern. "Although the totality of the data currently suggest that it is very unlikely that the signal in VSD represents true clinical risk, we believe it is important to share this information with the public," the health authorities said.

Open Forum

No items

Next Meeting Date

The next meeting is scheduled for April 28, 2023.

Adjourn

There being no further business, the meeting was adjourned at 2:48 p.m.

Approved: *David Moron*

David Moron, MD, Chairman

Minutes Prepared by:
Tonya Barrios, PhTR
Reviewed by:
Kasey L. Pena, PharmD

Appendix A

Meropenem (Merrem®)

Classification

Antibiotic, Carbapenem

Pharmacology

Meropenem is a broad-spectrum carbapenem antibiotic which is active against Gram-positive and Gram- negative bacteria. It exerts its mechanism of action by inhibiting bacterial cell wall synthesis by binding to several of the penicillin-binding proteins, which in turn inhibit the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis; bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Indication

Meropenem for injection (I.V) is a penem antibacterial indicated for the treatment of:

- Complicated skin and skin structure infections
- Complicated intra-abdominal infections
- Bacterial meningitis

Off labeled uses include the following: Anthrax, bloodstream infections, cystic fibrosis (acute pulmonary exacerbation), moderate to severe diabetic foot infections, intracranial abscess, or spinal epidural abscess, Melioidosis, Neutropenic enterocolitis, neutropenic fever, Osteomyelitis, Pneumonia, Prosthetic joint infection, Sepsis/septic shock, complicated urinary tract infection.

Pharmacokinetics

Pharmacokinetic Parameters	Details
Absorption	At the end of a 30-minute intravenous infusion of a single dose of meropenem in healthy volunteers, mean peak plasma concentrations of meropenem are approximately 23 mcg/mL (range 14-26) for the 500 mg dose and 49 mcg/mL (range 39-58) for the 1 gram dose. A 5-minute intravenous bolus injection of meropenem IV in healthy volunteers results in mean peak plasma concentrations of approximately 45 mcg/mL (range 18-65) for the 500 mg dose and 112 mcg/mL (range 83 140) for the 1 gram dose. Following intravenous doses of 500 mg, mean plasma concentrations of meropenem usually decline to approximately 1 mcg/mL at 6 hours after administration. No accumulation of meropenem in plasma was observed with regimens using 500 mg administered every 8 hours or 1 gram administered every 6 hours in healthy volunteers with normal renal function.

Pharmacokinetic Parameters	Details
Distribution	Well distributed into body tissues and fluid, including bronchial mucosa, lung, bile, gynecologic tissue (endometrium, myometrium, ovary, cervix, fallopian tube), muscle, heart valves, skin, urinary tract, bone, and interstitial and peritoneal fluid. Vd: Adults: 15-20L, Children 0.3 – 0.4 L/kg Protein binding is approximately 2%
Metabolism	Hepatic: hydrolysis of beta-lactam bond to open beta lactam from. There is one metabolite of meropenem that is microbiologically inactive
Excretion	Meropenem is primarily excreted unchanged by the kidneys. Approximately 70% (50-75%) of the dose is excreted unchanged within 12 hours. 28% is recovered as the microbiologically inactive metabolite. Fecal elimination is approximately 2% Urinary concentrations of meropenem are excess of 10mcg/mL are maintained for up to 5 hours after a 500mg dose.

Dosage/Administration

Adults: The usual dose is 500mg to 1 gram given by intravenous infusion every 8 hours, depending in large part on the type and severity of infection, the known suspected susceptibility of the pathogens and the condition of the patient. Doses up to 2g every 8 hours have been used.

Meropenem should be given by intravenous infusion over 15 to 30 minutes or as an intravenous bolus injection (5-20mL) over approximately 5 minutes.

When treating infections were Pseudomonas aeruginosa is known or suspected, a dose of at least 1g every 8 hours in adults (Max approved dose is 6 grams daily in 3 divided doses) is recommended.

Type of Infection	Dose	Dosage Interval
Complicated urinary tract	500 mg	every 8 hours
Uncomplicated skin and skin structure	500 mg	every 8 hours
Complicated skin and skin structure	500 mg	every 8 hours
Gynecologic and Pelvic Inflammatory Disease	500 mg	every 8 hours
Lower respiratory		
Community-acquired pneumonia	500 mg	every 8 hours
Nosocomial pneumonia	1 g	every 8 hours
Complicated intra-abdominal	1 g	every 8 hours
Meningitis	2 g	every 8 hours
Septicemia	1 g	every 8 hours

Renal Impaired Function: Dosage should be reduced in patients with creatinine clearance less than 51ml/min.

Creatinine clearance (mL/min)	Dose (dependent on type of infection)	Dosing Interval
26-50	recommended dose (500 mg to 2000 mg)	every 12 hours
10-25	one-half recommended dose	every 12 hours
<10	one-half recommended dose	every 24 hours

Meropenem is removed by hemodialysis and hemofiltration, if continued treatment with meropenem is necessary, the dose should be administered at the completion of the hemodialysis procedure.

Preparation and Administration: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Intravenous bolus Administration should be re-constituted with sterile water for injection, see below. Shake to dissolve and let stand until clear.

Vial Size	Amount of Diluent Added (mL)	Approximate Withdrawable Volume (mL)	Approximate Average Concentration (mg/mL)
500 mg	10	10	50
1 gram	20	20	50

For Infusion: Injection vials may be directly re-constituted with compatible infusion fluid, alternatively, an injection vial may be re-constituted, then the resulting solution added to an intravenous container and further diluted with an appropriate infusion fluid.

Stability and Storage: Freshly prepared solutions of Meropenem should be used. However, re-constituted solutions of Meropenem maintain satisfactory potency under the conditions described below. Solutions of intravenous Meropenem should not be frozen.

Intravenous Bolus Administration: Meropenem injection vials re-constituted with sterile Water for Injection for bolus administration (up to 50 mg/mL of Meropenem) may be stored for up to 3 hours at up to 25°C (77°F) or for 13 hours at up to 5°C (41°F).

Intravenous Infusion Administration: Solutions prepared for infusion (Meropenem concentrations ranging from 1 mg/mL to 20 mg/mL) re-constituted with Sodium Chloride Injection 0.9% may be stored for 1 hour at up to 25°C (77°F) or 15 hours at up to 5°C (41°F).

Solutions prepared for infusion (Meropenem concentrations ranging from 1 mg/mL to 20 mg/mL) re-constituted with Dextrose Injection 5% should be used immediately.

Typical Meropenem intravenous infusion delivery is 500mg or 1gram in 50ML NS.

Use in Special Population

Hepatic Impairment: No dose adjustments required.

Renal impairment: See dosage/administration.

Geriatric Patient: No dosage adjustments needed.

Pregnancy: Category B

Lactation: Not known whether distributed into milk. Use with caution.

Contraindication

Hypersensitivity (Immediate and delayed) to meropenem, other drugs in the same class, or any component of the formulation; patients who have experienced anaphylactic reactions to beta-lactams

Precautions

Hypersensitivity Reactions: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with β-lactams. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with another β-lactam. Before initiating therapy with meropenem, it is important to inquire about previous hypersensitivity reactions to penicillins, cephalosporins, other β-lactams, and other allergens. If an allergic reaction to meropenem occurs, discontinue the drug immediately.

Seizure Potential: Seizures and other adverse CNS experiences have been reported during treatment with meropenem. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) or with bacterial meningitis and/or compromised renal function). During clinical investigations, 2904 immunocompetent adult patients were treated for non-CNS infections with the overall seizure rate being 0.7% (based on 20 patients with this adverse event). All meropenem-treated patients with seizures had pre-existing contributing factors. Among these are included prior history of seizures or CNS abnormality and concomitant medications with seizure potential. Dosage adjustment is recommended in patients with advanced age and/or adult patients with creatinine clearance of 50 mL/min or less. Close adherence to the recommended dosage regimens is urged, especially in patients with known factors that predispose to convulsive activity. Continue anti-convulsant therapy in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, evaluate neurologically, placed on anti-convulsant therapy if not already instituted, and reexamine the dosage of meropenem to determine whether it should be decreased or discontinued.

Risk of Breakthrough Seizures Due to Drug Interaction with Valproic Acid: The concomitant use of meropenem and valproic acid or divalproex sodium is generally not recommended. Case reports in the literature have shown that co-administration of carbapenems, including meropenem, to patients receiving valproic acid or divalproex sodium results in a reduction in valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this

interaction, therefore increasing the risk of breakthrough seizures. Increasing the dose of valproic acid or divalproex sodium may not be sufficient to overcome this interaction. Consider administration of antibacterial drugs other than carbapenems to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium. If administration of meropenem is necessary, consider supplemental anti-convulsant therapy.

Clostridium difficile–associated Diarrhea: Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including meropenem, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing isolates of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

Development of Drug-Resistant Bacteria: Prescribing meropenem in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Overgrowth of Nonsusceptible Organisms: As with other broad-spectrum antibacterial drugs, prolonged use of meropenem may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

Thrombocytopenia: In patients with renal impairment, thrombocytopenia has been observed but no clinical bleeding reported.

Potential for Neuromotor Impairment: Alert patients receiving meropenem on an outpatient basis regarding adverse events such as seizures, delirium, headaches and/or paresthesia’s that could interfere with mental alertness and/or cause motor impairment. Until it is reasonably well established that meropenem is well tolerated, advise patients not to operate machinery or motorized vehicles.

Adverse Effects

The following adverse drug reactions and incidences are derived from product labeling unless otherwise specified.

- 1% to 10%:

    - Cardiovascular: Acute myocardial infarction (≤1%), bradycardia (≤1%), cardiac failure (≤1%), chest pain (≤1%), hypertension (≤1%), hypotension (≤1%), peripheral edema (≤1%), peripheral vascular disease (>1%), pulmonary embolism (≤1%), shock (1%), syncope (≤1%), tachycardia (≤1%)
    - Dermatologic: Dermal ulcer (≤1%), diaphoresis (≤1%), pruritus (1%), skin rash (2% to 3%, includes diaper-area moniliasis in infants), urticaria (≤1%)
    - Endocrine & metabolic: Hypervolemia (≤1%), hypoglycemia (>1%)
    - Gastrointestinal: Abdominal pain (≤1%), anorexia (≤1%), constipation (1% to 7%), diarrhea (4% to 7%), dyspepsia (≤1%), enlargement of abdomen (≤1%), flatulence (≤1%), gastrointestinal disease (>1%), glossitis (1%), intestinal obstruction (≤1%), nausea (≤8%), oral candidiasis (≤2%), vomiting (≤4%)
    - Genitourinary: Dysuria (≤1%), pelvic pain (≤1%), urinary incontinence (≤1%), vulvovaginal candidiasis (≤1%)
    - Hematologic & oncologic: Anemia (≤6%), hypochromic anemia (≤1%)
    - Hepatic: Cholestatic jaundice (≤1%), hepatic failure (≤1%), jaundice (≤1%)
    - Infection: Sepsis (2%)
    - Local: Inflammation at injection site (2%)
    - Nervous system: Agitation (≤1%), anxiety (≤1%), chills (≤1%), confusion (≤1%), delirium (≤1%), depression (≤1%), dizziness (≤1%), drowsiness (≤1%), hallucination (≤1%), headache (2% to 8%), insomnia (≤1%), nervousness (≤1%), pain (≤5%), paresthesia (≤1%), seizure (≤1%)
    - Neuromuscular & skeletal: Asthenia (≤1%), back pain (≤1%)
    - Renal: Renal failure syndrome (≤1%)
    - Respiratory: Apnea (1%), asthma (≤1%), cough (≤1%), dyspnea (≤1%), hypoxia (≤1%), pharyngitis (>1%), pleural effusion (≤1%), pneumonia (>1%), pulmonary edema (≤1%), respiratory system disorder (≤1%)
    - Miscellaneous: Accidental injury (>1%), fever (≤1%)
- <1%:
    - Cardiovascular: Local thrombophlebitis, localized phlebitis
    - Endocrine & metabolic: Edema at insertion site
    - Gastrointestinal: Gastrointestinal hemorrhage, melena
    - Hematologic & oncologic: Hemoperitoneum
    - Local: Injection site reaction, pain at injection site
    - Respiratory: Epistaxis
- Frequency not defined:
    - Endocrine & metabolic: Hypokalemia, increased lactate dehydrogenase
    - Genitourinary: Hematuria
    - Hematologic & oncologic: Decreased partial thromboplastin time, decreased prothrombin time, eosinophilia, quantitative disorders of platelets
- Post marketing:
    - Dermatologic: Acute generalized exanthematous pustulosis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
    - Gastrointestinal: *Clostridioides difficile* associated diarrhea

- Hematologic & oncologic: Agranulocytosis, hemolytic anemia, leukopenia, neutropenia, positive direct Coombs test, positive indirect Coombs test, thrombocytopenia
- Hypersensitivity: Anaphylaxis, angioedema
- Immunologic: Drug reaction with eosinophilia and systemic symptoms

Monitoring

Perform culture and sensitivity testing prior to initiating therapy. Monitor for signs of anaphylaxis during first dose. During prolonged therapy, monitor renal function, liver function, CBC. During outpatient use, monitor for neuromotor impairment and mental alertness.

Interactions

- Bacillus clausii: Antibiotics may diminish the therapeutic effect of Bacillus clausii. Management: Bacillus clausii should be taken in between antibiotic doses during concomitant therapy. *Risk D: Consider therapy modification*
- BCG (Intravesical): Antibiotics may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*
- BCG Vaccine (Immunization): Antibiotics may diminish the therapeutic effect of BCG Vaccine (Immunization). *Risk C: Monitor therapy*
- Cholera Vaccine: Antibiotics may diminish the therapeutic effect of Cholera Vaccine. Management: Avoid cholera vaccine in patients receiving systemic antibiotics, and within 14 days following the use of oral or parenteral antibiotics. *Risk X: Avoid combination*
- Fexinidazole: May increase the serum concentration of OAT1/3 Substrates (Clinically Relevant). Management: Avoid use of fexinidazole with OAT1/3 substrates when possible. If combined, monitor for increased OAT1/3 substrate toxicities. *Risk D: Consider therapy modification*
- Immune Checkpoint Inhibitors: Antibiotics may diminish the therapeutic effect of Immune Checkpoint Inhibitors. *Risk C: Monitor therapy*
- Lactobacillus and Estriol: Antibiotics may diminish the therapeutic effect of Lactobacillus and Estriol. *Risk C: Monitor therapy*
- Leflunomide: May increase the serum concentration of OAT1/3 Substrates (Clinically Relevant). *Risk C: Monitor therapy*
- Nitisinone: May increase the serum concentration of OAT1/3 Substrates (Clinically Relevant). *Risk C: Monitor therapy*
- Pretomanid: May increase the serum concentration of OAT1/3 Substrates (Clinically Relevant). *Risk C: Monitor therapy*
- Probenecid: May increase the serum concentration of Meropenem. *Risk X: Avoid combination*
- Sodium Picosulfate: Antibiotics may diminish the therapeutic effect of Sodium Picosulfate. Management: Consider using an alternative product for bowel cleansing prior to a colonoscopy in patients who have recently used or are concurrently using an antibiotic. *Risk D: Consider therapy modification*
- Taurursodiol: May increase the serum concentration of OAT1/3 Substrates (Clinically Relevant). *Risk X: Avoid combination*
- Teriflunomide: May increase the serum concentration of OAT1/3 Substrates (Clinically Relevant). *Risk C: Monitor therapy*
- Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. Management: Avoid

use of live attenuated typhoid vaccine (Ty21a) in patients being treated with systemic antibacterial agents. Postpone vaccination until 3 days after cessation of antibiotics and avoid starting antibiotics within 3 days of last vaccine dose. *Risk D: Consider therapy modification*

- Valproate Products: Carbapenems may decrease the serum concentration of Valproate Products. Management: Concurrent use of carbapenem antibiotics with valproic acid is generally not recommended. Alternative antimicrobial agents should be considered, but if a concurrent carbapenem is necessary, consider additional anti-seizure medication. *Risk D: Consider therapy modification*

Efficacy

Complicated Skin and Skin Structure Infections

Adult patients with complicated skin and skin structure infections including complicated cellulitis, complex abscesses, perirectal abscesses, and skin infections requiring intravenous antimicrobials, hospitalization, and surgical intervention were enrolled in a randomized, multi-center, international, double-blind trial. The study evaluated meropenem at doses of 500 mg administered intravenously every 8 hours and imipenem-cilastatin at doses of 500 mg administered intravenously every 8 hours. The study compared the clinical response between treatment groups in the clinically evaluable population at the follow-up visit (test-of-cure). The trial was conducted in the United States, South Africa, Canada, and Brazil. At enrollment, approximately 37% of the patients had underlying diabetes, 12% had underlying peripheral vascular disease and 67% had a surgical intervention. The study included 510 patients randomized to meropenem and 527 patients randomized to imipenem-cilastatin. Two hundred and sixty-one (261) patients randomized to meropenem and 287 patients randomized to imipenem-cilastatin were clinically evaluable. The success rates in the clinically evaluable patients at the follow-up visit were 86% (225/261) in the meropenem arm and 83% (238/287) in imipenem-cilastatin arm.

Complicated Intra-Abdominal Infections

One controlled clinical study of complicated intra-abdominal infection was performed in the United States where meropenem was compared with clindamycin/tobramycin. Three controlled clinical studies of complicated intra-abdominal infections were performed in Europe; meropenem was compared with imipenem (two trials) and cefotaxime/metronidazole (one trial). Using strict evaluability criteria and microbiologic eradication and clinical cures at follow-up which occurred 7 or more days after completion of therapy, the presumptive microbiologic eradication/clinical cure rates and statistical findings are as follows:

Treatment Arm	No. evaluable/ No. enrolled (%)	Microbiologic Eradication Rate	Clinical Cure Rate	Outcome
meropenem	146/516 (28%)	98/146 (67%)	101/146 (69%)	
imipenem	65/220 (30%)	40/65 (62%)	42/65 (65%)	meropenem equivalent to control
cefotaxime/ metronidazole	26/85 (30%)	22/26 (85%)	22/26 (85%)	meropenem not equivalent to control
clindamycin/ tobramycin	50/212 (24%)	38/50 (76%)	38/50 (76%)	meropenem equivalent to control

Bacterial Meningitis

Four hundred forty-six patients (397 pediatric patients 3 months to less than 17 years of age) were enrolled in 4 separate clinical trials and randomized to treatment with meropenem (n=225) at a dose of 40 mg/kg every 8 hours or a comparator drug, i.e., cefotaxime (n=187) or ceftriaxone (n=34), at the approved dosing regimens. A comparable number of patients were found to be clinically evaluable (ranging from 61-68%) and with a similar distribution of pathogens isolated on initial CSF culture.

Patients were defined as clinically not cured if any one of the following three criteria were met:

1. At the 5-7 week post-completion of therapy visit, the patient had any one of the following: moderate to severe motor, behavior or development deficits, hearing loss of greater than 60 decibels in one or both ears, or blindness.
2. During therapy the patient's clinical status necessitated the addition of other antibacterial drugs.
3. Either during or post-therapy, the patient developed a large subdural effusion needing surgical drainage, or a cerebral abscess, or a bacteriologic relapse. Using the definition, the following efficacy rates were obtained, per organism). The values represent the number of patients clinically cured/number of clinically evaluable patients, with the percent cure in parentheses.

Efficacy Rates by Pathogen in the clinically Evaluable Population with Bacterial Meningitis

MICROORGANISMS	MERREM IV	COMPARATOR
S. pneumoniae	17/24 (71)	19/30 (63)
H. influenzae (+)[1]	8/10 (80)	6/6 (100)
H. influenzae (-/NT)[2]	44/59 (75)	44/60 (73)
N. meningitidis	30/35 (86)	35/39 (90)
Total (including others)	102/131 (78)	108/140 (77)

1. (+) β-lactamase-producing
2. (-/NT) non-β-lactamase-producing or not tested

Dosage Forms/Cost (AWP)

- Meropenem 1G/30ML Vial CT 10 $132-$360
- Meropenem 500mg/20ML Vial CT 10 $36-$174.60
- Meropenem 500mg/50ML NS Bags CT 24 $561.89
- Meropenem 1G/50ML NS Bags CT 24 $839.52

Summary/Conclusion

Meropenem is stable antibiotic used for a variety of infections. It has high quality trials justifying its use, with an acceptable safety profile. Currently, there are no carbapenems on the formulary to treat infection. It niche from the SSLC side would be to provide continuation of therapy post hospital discharge.

Recommendation

Recommend adding meropenem 500mg and 1g in both vial and premixed bag form.

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Appendix B

Pimavanserin (Nuplazid®)

Classification[1]

Atypical antipsychotic

Pharmacology[1,2]

Pimavanserin is metabolized to an active N-desmethylated metabolite (AC-279). This medication acts as an inverse agonist and antagonist with high affinity for serotonin Type 2A (5-HT2A) receptors and a lower affinity for serotonin Type 2C (5-HT2C) receptors. It also has some low binding affinity to sigma 1 receptors. Pimavanserin has no appreciable affinity for serotonin Type 2B (5-HT2B), dopaminergic (including D2), muscarinic, histaminergic, or adrenergic receptors, or to calcium channels.

Black Box Warning[1]

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Pimavanserin is not approved for use in patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis.

Indication[1]

Pimavanserin is FDA approved for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

Pharmacokinetics[1]

Pharmacokinetic Parameter	Details
Absorption	• Median T_{max} was 6 hours (range 4-24 hours) and generally unaffected by dose • Formation of the major circulating *N*-desmethylated active metabolite (AC-279) from pimavanserin occurs with a median T_{max} of 6 hours • Ingestion of a high-fat meal had no significant effect on rate (C_{max}) and extent (AUC) of pimavanserin exposure - C_{max} decreased by about 9% while AUC increased by about 8% with a high-fat meal
Distribution	• Highly protein bound (~95%) in human plasma • Protein binding appeared to be dose-independent and did not change significantly over dosing time from Day 1 to Day 14 • Volume of distribution is 2,173 L ± 307 after a single dose of pimavanserin 34 mg

Pharmacokinetic Parameter	Details
Metabolism	• Predominately metabolized by CYP3A4 and CYP3A5 and to a lesser extent by CYP2J2, CYP2D6, and various other CYP and flavin-containing monooxygenase (FMO) enzymes • CYP3A4 is the major enzyme responsible for the formation of pimavanserin's major active metabolite (AC-279) • Pimavanserin does not cause clinically significant inhibition or induction of CYP3A4
Excretion	• 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 • Less than 1% of the administered dose of pimavanserin and its active metabolite (AC-279) were recovered in the urine • Half-life: ~57 hours (pimavanserin); ~200 hours (AC-279, active metabolite)

Dosage/Administration[1]

Pimavanserin is dosed at 34mg orally once daily, without need for titration. It may be taken with or without food.

The dose of pimavanserin should be reduced to 10mg orally once daily when co-administered with strong CYP3A4 inhibitors.

Avoid concomitant use of strong CYP3A4 inducers with pimavanserin.

The capsule may be taken whole or opened and the entire contents sprinkled over a tablespoon of applesauce, yogurt, pudding, or a liquid nutritional supplement. Consume the drug/food mixture immediately without chewing; do not store for future use.

Use in Special Populations[1]

Pregnancy: There is no data on pimavanserin use in pregnant women that would allow for assessment of the drug-associated risk of major malformations or miscarriage. Data from animal reproduction studies has been variable. One study showed no adverse developmental effects in rabbits who received doses up to 10- or 12-times the maximum recommended human dose (MRHD) of 34 mg/day during the period of organogenesis, but other studies have shown maternal toxicity including mortality, dehydration, decreased pup survival, reduced litter size, and reduced pup weight when doses above the MRHD were administered.

Lactation: There is no information regarding the presence of pimavanserin in human milk, the effects on the breastfed infant, or the effects on milk production.

Pediatric: Safety and efficacy of pimavanserin has not been established in pediatric patients.

Geriatric: No dosage adjustment is required for elderly patients.

Renal Impairment: No dosage adjustment is necessary in patients with mild to severe renal impairment or in end stage renal disease. However, pimavanserin should be used with caution in patients with severe renal impairment or end stage renal disease due to possible increased exposure in these patients.

Hepatic Impairment: No dosage adjustment is required for patients with hepatic impairment.

Contraindication[1]

Patients with known hypersensitivity to pimavanserin or any components of the formulation should not receive this medication.

Precautions[1,2]

- Increased mortality in elderly patients with dementia-related psychosis (boxed warning)
- QTc prolongation
- Central nervous system (CNS) depression, which may impair physical or mental abilities
- Esophageal dysmotility/aspiration
- Falls
- Orthostatic hypotension

Adverse Effects[1]

The following adverse reactions are based on the 6-week, placebo-controlled studies in which pimavanserin was administered once daily to patients with hallucinations and delusions associated with Parkinson's disease.

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

Adverse Effect	Pimavanserin 34 mg (N=202)	Placebo (N=231)
Peripheral edema	7%	2%
Confusional state	6%	3%

Adverse Reactions with Incidence ≥2% and > Placebo

Gastrointestinal disorders	Pimavanserin 34 mg (N=202)	Placebo (N=231)
Nausea	7%	4%
Constipation	4%	3%

General Disorders	Pimavanserin 34 mg (N=202)	Placebo (N=231)
Peripheral edema	7%	2%
Gait disturbance	2%	<1%

Psychiatric disorders	Pimavanserin 34 mg (N=202)	Placebo
Hallucinations	5%	3%
Confusional state	6%	3%

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

Monitoring[2]

- Monitor for improvement in hallucinations and delusions and the need for continued treatment.
- While preliminary research indicates tolerability to pimavanserin and the manufacturer does not require specific monitoring, it is recommended that the atypical antipsychotic audit criteria monitoring parameters be followed.

Interactions[1]

QTc Prolongation:

- Concomitant use of medications that prolong the QT interval may add to the QT effects of pimavanserin and increase the risk of cardiac arrhythmia.
- Avoid 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.
- Reduce dose of pimavanserin to 10mg/day if a strong CYP3A4 inhibitor (including itraconazole, ketoconazole, clarithromycin, indinavir) is used concomitantly with pimavanserin.

Moderate or Strong CYP3A4 Inducers:

- Concomitant use of pimavanserin with a moderate or strong CYP3A4 inducers reduces pimavanserin exposure.
- Avoid use of moderate (modafinil, thioridazine, efavirenz, nafcillin) or strong (carbamazepine, St. John's Wort, phenytoin, rifampin) CYP3A4 inducers with pimavanserin.

Efficacy

Parkinson's Disease Psychosis: Arcadia Pharmaceuticals completed several studies before receiving Food and Drug Administration (FDA) approval for pimavanserin for the indication of Parkinson's disease psychosis (PDP). Initial studies (ACP-103-006, ACP-103-012, ACP-103-014; referred to as 006, 012, and 014, respectively) failed to demonstrate statistically significant improvements. However, after presenting the positive findings of ACP-103-020 (referred to as study 020), the FDA granted approval for pimavanserin for the treatment of PDP in April 2016.

Study 006[3]: Study 006 was a phase 2, multi-centered, randomized, placebo-controlled, double-blind, proof of concept study. Patients in this trial received study drug or placebo daily for 4 weeks, starting with 17 mg on day 1, with possible increases to 34 mg on day 8 and 51 mg on day 15 based on clinical response. Patients were evaluated at baseline and on study days 1, 8, 15, and 28 (and day 57 for 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. Additionally, investigators assessed SAPS domain scores for hallucinations and delusions, and utilized the combination of these 2 domain scores 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 7 items – total score) and a sum of SAPS delusions score (sum of all 13 items – total score). This SAPS total domain score was chosen as the primary efficacy outcome measure.

60 patients with moderate-to-severe PDP were enrolled into the study (n=29 pimavanserin, n=31 placebo). 20 patients in the pimavanserin group and 24 patients in the placebo group completed the study. While some subscales did show significant improvements, results for the primary outcome found that pimavanserin failed to show a statistically significant improvement compared to placebo (p=0.09, effect size=0.52).

Studies 012 and 014[4,5,6]: 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 in the U.S., Europe, and India. The primary outcome measure was SAPS - hallucinations + delusions (SAPS H+D). Upon completion of the study, results found that pimavanserin failed to demonstrate a statistical difference over placebo (SAP H+D least-squares [LS] mean difference from baseline vs. placebo for 10 mg [-0.07, 95% CI -1.7-1.59] and 40 mg [-1.16, 95% CI -2.83-0.51]). Investigators attributed this outcome 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 the investigators deciding that the study was unlikely to demonstrate efficacy due to lack of significant improvement found in study 012.

Study 020[7]: Study 020 made several design changes based on the previously failed studies. This trial was completed in the U.S. and Canada, utilized centralized raters for evaluating the primary efficacy outcome, exclusively used pimavanserin tartrate 40 mg (equivalent to pimavanserin 34 mg), reduced the frequency of visits and treatment arms, and implemented a two-week lead-in period of psychosocial therapy to blunt the placebo response. Investigators also identified a different primary outcome, the Scale for Assessment of Positive Symptoms – Parkinson Disease (SAPS-PD), which focused on the SAPS subdomains for hallucinations and delusions. From these subdomains, the SAPS-PD uses 5 of the 7 items in the hallucinations subdomain and 4 of the 13 items from the delusions subdomain. Patients in this study were randomized and then entered into a two-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. After screening 314 participants, 199 patients were allocated to treatment and 185 patients were included in the full analysis set.

In the primary analysis, the pimavanserin group exhibited significant improvement in SAPS-PD score compared to placebo at day 43 (-5.79 vs. -2.73% p=0.0006). Furthermore, 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) and CGI-S (effect size 0.52, p=0.0007). Exploratory analyses also 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).

Extension Studies: Ballard, et al (2015)[8] completed a post hoc analysis of data from a multicenter, open-label extension (OLE) study of pimavanserin comparing patients taking and not taking concurrent antipsychotics. The analysis included 423 patients, 66 (15.6%) of whom received an add-on antipsychotic medication during the study period. The majority of patients prescribed an add-on antipsychotic were taking quetiapine (79%) at daily doses of 25-50 mg (range 12.5-350 mg).

Safety assessments were completed at 2 weeks, 1, 3, 6, 9, and 12 months, and then every 6 months thereafter. Results found a significant increase in mortality for patients taking a concomitant antipsychotic medication compared to those who were not (IRR 4.20, 95% CI 2.13-7.96). Patients who received concomitant antipsychotic medication were significantly more likely to experience 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 was not statistically significant.

Isaacson, et al (2021)[9] completed a multicenter, OLE study in 459 patients who previously completed one of the three 6-week double-blind, placebo-controlled studies (012, 014, or 020). Patients were given pimavanserin 34 mg/day with the goal of assessing sustained response 4 weeks after the completion of the previous placebo-controlled study (patients remained blinded to the original treatment allocation from their previous double-blind study). The primary endpoint was the SAPS-PD (the same as the previous studies' primary endpoint).

In the patients entering the OLE study who had received placebo during their previous study, the mean change from OLE baseline to OLE week 4 in the SAPS-PD was -2.9. For participants previously dosed with pimavanserin 34 mg, the mean change from OLE baseline to OLE week 4 for the SAPS-PD was -0.8. These findings supported the efficacy of pimavanserin in treating hallucinations and delusions associated with PDP for up to 10 weeks.

Dementia-Related Psychosis: Arcadia Pharmaceuticals sought FDA approval for pimavanserin for the treatment of Alzheimer's disease psychosis (ADP). After presenting the results of two studies (Study 019 and NCT03325556), the FDA denied approval for the ADP indication in August 2022 and suggested that the company conduct an additional trial.

Study 019[10]: Study 019 was a phase 2, randomized, double-blind, placebo-controlled trial completed in the UK to assess the safety, tolerability, and efficacy of pimavanserin in patients with ADP. Patients with possible or probable Alzheimer's disease and psychotic symptoms including visual or auditory hallucinations, delusions, or both were randomly assigned (1:1) to receive pimavanserin 34 mg/day

or placebo. The primary endpoint was mean change from baseline to week 6 in the Neuropsychiatric Inventory-Nursing Home Psychosis Score (NPI-NH-PS) in the modified intention-to-treat population.

181 patients were randomly assigned to treatment (n=90 pimavanserin, n=91 placebo). The mean change in NPI-NH-PS at week 6 was -3.76 for pimavanserin and -1.93 for placebo (mean difference -1.84 [95% CI -3.64 to -0.004], Cohen's d=-0.32, p=0.045). However, by week 12, no significant advantage for pimavanserin versus placebo was observed (treatment difference -0.51 [95% CI -2.23 to 1.21]; p=0.561).

NCT332556[11]: NCT332556 was a phase 3, double-blind, placebo-controlled discontinuation trial that included patients with dementia-related psychosis. Patients received open-label pimavanserin 20-34 mg/day for 12 weeks. Those who had a reduction from baseline of at least 30% in SAPS H+D score and a CGI-I score of 1 (very much improved) or 2 (much improved) at weeks 8 or 12 were then randomly assigned (1:1) to pimavanserin or placebo for up to 26 weeks. The primary end point, assessed in a time-to-event analysis, was relapse of psychosis as defined by at least 30% increase in SAPS-H+D score and a CGI-I score of 6 (much worse) or 7 (very much worse), hospitalization for dementia-related psychosis, stopping the trial regimen or withdrawal from trial for lack of efficacy, or use of another antipsychotic agent for dementia-related psychosis.

392 patients were enrolled in the open-label pimavanserin phase of the trial, which included patients with Alzheimer's disease (66.3%), Parkinson's disease dementia (15.1%), dementia with Lewy bodies (7.1%), frontotemporal dementia (1.8%), and vascular dementia (9.7%). 41 patients withdrew from the trial for administrative reasons, and 134 patients discontinued due to lack of response (n=70), adverse effect (n=27), withdrew consent (n=17), non-adherence (n=5), protocol violation (n=4), death (n=1), lost to follow-up (n=1), received prohibited medication (n=1), other (n=8). The mean reduction in SAP H+D score from baseline in those who made it to week 8 or 12 was 75.2%.

217 patients met criteria to move on and undergo randomization at week 8 or 12 (n= 105 pimavanserin, n=112 placebo). By the end of the trial, 72 patients (26 in the pimavanserin group and 46 in the placebo group) had discontinued the trial and 66 (35 in the pimavanserin group and 31 in the placebo group) were withdrawn for administrative reasons due to the trial being stopped early for efficacy. For those who entered this double-blind portion of the trial, the frequency of relapse was 13% in the pimavanserin group and 28% in the placebo group (HR for time to relapse, 0.35; 95% CI, 0.17-0.73; P=0.005). Trial discontinuation during this phase was 21 patients (22%) in the pimavanserin group and 38 patients (38%) in the placebo group (HR for time to trial discontinuation for any reason 0.45; 95% CI, 0.26-0.79; P=0.005).

Adverse effects during the open-label phase occurred in 142 (36.2%) of patients. Such events that occurred in >2% of patients were urinary tract infection (5.1%), constipation (2.6%), and hypertension (2.3%). One patient died from suspected myocardial infarction that was considered by the investigator to be unrelated to pimavanserin. Among all the patients who received pimavanserin during the trial, the most common adverse events were constipation (3.1%), headache (4.1%), and urinary tract infection (6.4%). Mean change in QTc of those who were exposed to pimavanserin was 5.4 msec. A total of five adverse events involving asymptomatic QTc prolongation were reported with pimavanserin during the entire trial, affecting 1.3% of the patients.

After reviewing this trial, the FDA acknowledged the positive results but stated that the data appeared to be driven primarily by the robust findings in the subgroup of individuals with Parkinson's disease dementia.[12]

Additional ADP Study: Ballard, et al (2019)[13] completed a subgroup analysis in the patients with possible or probable Alzheimer's disease from Study 019 to assess the mean change in NPI-NH-PS in those with more pronounced psychotic symptoms. 57 patients with a baseline NPI-NH-PS >12 (n=27 pimavanserin, n=30 placebo) were included in this analysis. The authors found that 88.9% in the pimavanserin group vs. 43.3% in the placebo group had >30% improvement in NPI-NH-PS ($p<0.001$), and that 77.8% in the pimavanserin group vs. 43.3% in the placebo group had >50% improvement in NPI-NH-PS ($p=0.008$). The rate of adverse events in this severe patient subgroup was similar between treatment groups, with urinary tract infection, falls, and agitation being the most frequent.

Studies for Other Indications: Nasarallah, et al (2019)[14] completed a study reviewing 10 cases where pimavanserin was used in patients with refractory hallucinations and delusions who failed to respond to clozapine. The authors reported that all 10 patients showed marked response to pimavanserin 34 mg/day within 4-8 weeks but did note the need for controlled studies comparing clozapine and pimavanserin in refractory schizophrenia to confirm these clinical observations.

Metzler, et al (2012)[15] completed a multicenter, randomized, double-blind trial over 6 weeks in 423 patients with chronic schizophrenia experiencing a recent exacerbation of psychotic symptoms. Patients were randomized to risperidone 2 mg + placebo (RIS2PBO), risperidone 2 mg + pimavanserin 20 mg (RIS2PIM), risperidone 6 mg + placebo (RIS6PBO), haloperidol 2 mg + placebo (HAL2PBO), or haloperidol 2 mg + pimavanserin 20 mg (HAL2PIM). The authors found that patients in the RIS2PIM group had a significantly greater reduction in Positive and Negative Syndrome Scale (PANSS) Total Score compared to the RIS2PBO group (-23.0 vs -16.3, $p=0.007$) and that the percentage of patients with >20% improvement at day 15 was significantly higher in the RIS2PIM group compared to the RIS6PBO group (62.3% vs 42.1%; $p=0.01$). HAL2PBO vs HAL2PIM and RIS2PIM vs RIS6PBO were not significantly different from each other in efficacy. The authors concluded that a sub-effective

risperidone dose combined with pimavanserin to enhance 5-HT_{2A} blockade provided faster onset of action, equal efficacy, and better safety compared to the standard risperidone dose.

Fava, et al (2019)[16] completed a phase 2, randomized, double-blind, placebo-controlled study of adjunctive pimavanserin in patients with major depressive disorder with inadequate response to a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI). Using a 2-stage sequential parallel-comparison design, 207 patients were initially randomized in a 3:1 ratio to placebo or pimavanserin added to ongoing SSRI or SNRI therapy; at 5 weeks, placebo non-responders were re-randomized to placebo or pimavanserin for an additional 5 weeks. The authors found that those who received pimavanserin had a statistically significant improvement in the Hamilton Rating Scale for Depression 17-item version (HAM-D-17) and Sheehan Disability Scale (SDS) score over placebo from baseline. However, Dirks, et al (2022)[17] published the combined results from two randomized, double-blind, placebo-controlled phase 3 studies that looked at pimavanserin as an adjunctive treatment for patients with major depressive disorder. In both studies, patients were randomly assigned 1:1 to pimavanserin or placebo to be added to current antidepressant therapy. The authors found that pimavanserin did not provide a significant improvement in the HAM-D-17 over placebo from baseline to week 5.

Ongoing and Future Studies[18]

Study Title	Status
Pimavanserin in Irritability Associated with Autism Spectrum Disorder	Recruiting
Extension Study of Pimavanserin in Irritability Associated with Autism Spectrum Disorder	Recruiting
Pimavanserin for Insomnia in Veterans with Posttraumatic Stress Disorder (PTSD): Proof of Concept	Not Yet Recruiting
Extension Study of Pimavanserin for Adjunctive Treatment for Schizophrenia	Recruiting
Pimavanserin for Insomnia in Veterans with PTSD	Not yet Recruiting
Extension Study of Pimavanserin in Adult Subjects with Neuropsychiatric Symptoms Related to Neurodegenerative Disease	Active, No Recruiting
Pimavanserin vs. Quetiapine for Treatment of Parkinson's Psychosis	Recruiting

Study Title	Status
Efficacy and Safety of Pimavanserin in Adjunctive Treatment for Negative Symptoms of Schizophrenia	Recruiting
Randomized Placebo Controlled Trial Evaluating the Efficacy of Pimavanserin, a Selective Serotonin 5-HydroxyTryptamine-2A (5HT2A) Inverse Agonist, to treat Impulse Control Disorders in Parkinson's Disease	Recruiting
Comparing Antipsychotic Medication in Lewy Body Dementia Over Time	Recruiting
Pimavanserin Treatment in Tourette Syndrome	Completed, No Results Posted

Dosage Forms/Cost (AWP)

Name	Dosage Form	Strength	AWP
Pimavanserin	Tablet	10 mg	$5478.00 (bottle of 30)
Pimavanserin	Capsule	34 mg	$5478.00 (bottle of 30)

For outpatient coverage, the manufacturer offers comprehensive coverage and financial assistance support through Arcadia Connect™. Per the manufacturer's website, this program can provide resources to help patients access and afford their medication. Nuplazid® is covered by 100% of Medicare Part D plans. For patients who do not have insurance or their insurance does not cover their prescription, they may be able to receive Nuplazid® for $0 through the Arcadia Connect™ Patient Assistance Program.[19]

Summary/Conclusion

Pimavanserin is the only medication currently FDA-approved for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP). Arcadia Pharmaceuticals recently attempted to gain FDA approval for pimavanserin for the treatment of Alzheimer's disease psychosis (ADP). However, after reviewing the data submitted, the FDA denied approval for the ADP indication in August 2022 and suggested that the company conduct an additional trial. Other data has been published and demonstrated promising results for off-label indications, including use of pimavanserin for refractory hallucinations and delusions in patients who failed to respond to clozapine and adjunct pimavanserin in patients with chronic schizophrenia experiencing a recent exacerbation of psychotic symptoms.14,15 Furthermore, according to clinicaltrials.gov, there are several ongoing studies looking at the use of

pimavanserin in autism spectrum disorder, PTSD, Lewy Body dementia, and Tourette syndrome.[18]

While pimavanserin does have FDA approval for PDP, its efficacy has not been studied against other antipsychotics (i.e. quetiapine and clozapine) that are commonly utilized for this indication. Pimavanserin, along with all other antipsychotics, also carries a black box warning for increased risk of death in elderly patients with dementia-related psychosis. Additionally, the cost of pimavanserin is much higher than alternative treatment options.

Recommendation

At this time, it is recommended not to add pimavanserin to the formulary. If a provider would like to use this medication for PDP or another off-label indication, pimavanserin can be requested through the non-formulary process.

It is recommended that the literature be reviewed on a periodic basis for additional data on the safety and efficacy of pimavanserin.

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