Health and Specialty Care System
Executive Formulary Committee Minutes

Date

The Executive Formulary Committee convened on January 11, 2019 in Room 125 - ASH Building 552. The meeting was called to order by Dr. Messer, Chair at 9:40 a.m.

Jean Baemayr, PharmD- secretary	√	Ashton Wickramasinghe, MD	Absent
John Bennett, M.D.	√	Vacant- local authority practitioner	
Bonnie Burroughs, PharmD	√	Vacant- local authority practitioner	
Barbara Carroll, RN	Absent	Tim Bray (non-voting)	Absent
Cleveland "Chip" Dunlap, RN	√	Connie Horton, RNP (non-voting)	Absent
Catherine Hall, PharmD	√	Raul Luna, RN, MSN (non-voting)	Absent
Jeanna Heidel, PharmD	By Phone	Mike Maples (non-voting)	Absent
N. Kubista, DO	Absent	Nina Muse, M.D. (non-voting)	Partial
Jeff Matthews, MD	Absent	Peggy Perry (non-voting)	Absent
Mark Messer, DO- Chair	√	Rachel Samsel, (non-voting)	Absent
Scott Murry, MD	√	E. Ross Taylor, MD (non-voting)	√
Kenda Pittman, PharmD	√	.	
Rishi Sawhney, MD	√	.	
Glenn Shipley, DO	√	.	

Guests Present: Lisa Mican, PharmD, Pharmacy Director Austin State Hospital; Melanie Chang, ASH Pharmacy Intern; Raeschell Williams, PharmD, PGY2 VA Pharmacy Resident

Introduction and Other Information

Dr. Messer welcomed the committee members.

Approval of Minutes of October 5, 2018

On a motion of Dr. Bennett, seconded by Dr. Messer, the minutes of the October 5, 2018 meeting were approved as previously distributed.

Conflict of Interest

The Executive Formulary Committee Conflict of Interest Policy was distributed to the Committee members prior to the meeting. Voting committee members are

required to submit annual disclosures. The following individuals have submitted their statements and indicated no conflicts of interest:

Jean Baemayr
John Bennett
Bonnie Burroughs
Barbara Carroll
Cleveland "Chip" Dunlap
Catherine Hall
Mark Messer
Scott Murry
Kenda Pittman
Rishi Sawhney
Glenn Shipley
The following member's disclosure statements are pending:
Jeanna Heidel
Nikolaus Kubista
Jeffery Matthews
Ashton Wickramasinghe

Old Business

Psychotropic medication utilization parameters for children & youth (April 2018)

Dr. Muse presented a draft of the *Psychotropic Medication Utilization Parameters for Children and Youth in Texas Public Behavioral Health,* produced by the EFC workgroup. Among the differences between this document and the previous version are:

- increased emphasis on other treatment to be used in conjunction with medication
- increased emphasis on trauma-informed treatment
- more language and information related to medication use in preschoolers
- new tables on taper and titration guidance
- new tables on levels of evidence related to efficacy

The committee members were encouraged to conduct a more thorough review outside of the committee and send any comments to Dr. Muse. Dr. Hall recommended that sertraline be added to the list of antidepressants that can cause QTc prolongation. Dr. Muse will distribute the document to community academic partners for comment.

On a motion of Dr. Pittman, seconded by Dr. Messer, the *Psychotropic Medication Utilization Parameters for Children and Youth in Texas Public Behavioral Health*

draft document was approved, with the understanding that a final draft will be presented to the committee for approval at a later date.

TAC Title 25, Part 1, Chapter 415, Subchapter C (April 2017)

The work group appointed by the committee has not met. A new workgroup to review Chapter 415 in its entirety is currently being assigned by HHSC Medical and Social Services Division.

Psychotropic audit criteria & guidelines development- chemical dependency adjunct (January 2012)

Dr. Williams presented audit criteria for acamprosate, disulfiram, topiramate, naltrexone, buprenorphine, and buprenorphine/naloxone.

The committee made the following recommendations:

- Change references to alcohol or opioid dependence to alcohol or opioid use disorder.
- Clarify that "failed naloxone challenge test" as an absolute contraindication to naltrexone use only refers to the extended release injection formulation (Vivitrol®).

On a motion of Dr. Bennet, seconded by Dr. Messer, the Audit Criteria & Guidelines were approved with the above revisions. The audit criteria and checklist will be available on the EFC "Medication Audit Criteria and Checklists" webpage.

Psychotropic audit criteria & guidelines review-antidepressants (April 2012)

Dr. Hall presented audit criteria for bupropion, duloxetine, trazodone, and the SSRI's citalopram, escitalopram, fluoxetine, and sertraline. The committee discussed indications listed in the audit guidelines and clarified that they are intended to be FDA approved indications as well as off-label indications supported by literature and approved by the EFC.

The committee made the following recommendations:

- Bupropion:
    - Remove "off-label" comment on attention-deficit/hyperactivity disorder indication.
    - Add "activation" to list of adverse reactions.
    - Remove narrative sentences from Pregnancy use, leaving "Pregnancy category C. See section 8.1 of package insert."
    - Add "blood pressure prior to starting treatment and periodically throughout" to patient monitoring.
- Duloxetine:

    - Change indications for "Major Depressive Disorder (MDD)" and "Generalized Anxiety Disorder (GAD)" to "depressive disorders" and "anxiety disorders."
    - Add to drug interactions section "serotonergic drugs (SSRIs, SNRIs, triptans, TCAs, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, St. John's wort)."
- Trazodone:
    - Change indication for "depression" to "depressive disorders". Add "insomnia."
    - Add "at baseline and as clinically indicated" to CBC monitoring
- Citalopram:
    - Change indication for "Major Depressive Disorder (MDD)" to "depressive disorders." Add "anxiety disorders."
    - Add "EKG at baseline and as clinically indicated" to monitoring
- Escitalopram:
    - Change "Acute and Maintenance Treatment of Major Depressive Disorder (MDD)" to "depressive disorders." Change "Acute Treatment of Generalized Anxiety Disorder (GAD)" to "anxiety disorders."
    - Add "EKG at baseline and as clinically indicated" to monitoring
- Fluoxetine:
    - Change "Acute and Maintenance Treatment of Major Depressive Disorder (MDD)" to "depressive disorders in adults and children $\geq$ 8 years of age." Add "adults and children $\geq$ 7" to OCD indication. Add "Premenstrual dysphoric disorder (PMDD)" to indications. Remove "Acute treatment of Panic disorder, with or without agoraphobia." Add "anxiety disorders."
    - Add "EKG as clinically indicated" to monitoring
- Sertraline:
    - Change "Major depressive disorder (MDD)" to "depressive disorders." Add "adults and children $\geq$6" to OCD indication. Remove "Panic Disorder (PD)" and "Social Anxiety Disorder (SAD)". Add "anxiety disorders."
    - Add "EKG as clinically indicated" to monitoring

There are separate audit criteria and guidelines reviews pending for the following categories: amoxapine, mirtazapine, venlafaxine, SSRI's (paroxetine, fluvoxamine), MAOI's, and TCA's. These were all last updated in 2006.

On a motion of Dr. Sawhney, seconded by Dr. Messer, the Audit Criteria & Guidelines were approved with the above revisions. The audit criteria and checklist will be available on the EFC "Medication Audit Criteria and Checklists" webpage.

New Business

Adverse Drug Reaction Reports

The Executive Formulary Committee discussed two adverse drug reaction reports that was received from the field. Both adverse events were reported to the FDA's MedWatch program.

1. A 20-year-old female was admitted on November 2017. Her current diagnosis was schizoaffective disorder bipolar type, moderate IDD, and possible autism spectrum disorder. Since admission, the patient was stabilized on olanzapine 10mg PO QAM, 10mg PO Q 1pm and 10mg PO QHS, divalproex 1,000 mg BID and lamotrigine 100 mg daily. Baseline platelets at admission were 234,000. One week after initiating divalproex, her platelet count was 284,000. After titrating divalproex up to 1,000mg BID, her platelet count was 235,000. Lamotrigine was initiated March 2018. In April 2018, her platelet count dropped to 207,000, and in June 2018, her platelet count was 173,000. Although there is a notable trend of declining platelets, her platelet count was still within normal range. In July 2018, she was initiated on oral contraceptive, Nortrel, for menstrual cycle regulation. At the end of July 2018, she was suspected to have cellulitis and was prescribed sulfamethoxazole/trimethoprim 800-160mg PO BID for 10 days. On day 7 of SMZ-TMP treatment, the patient was noted to be "listless and drowsy with decreased appetite and feeling cold." On day 8 of SMZ-TMP treatment, she was noted to be shaky, drowsy, and pale and having difficulty breathing. Her temperature was 102.1 F and O2sat was 85%. Patient was given oxygen at 4L/min and acetaminophen for fever. O2sat and temperature returned to normal, but she still appeared weak and was transferred to another hospital for medical care. On day 1 at the medical facility, she was febrile and empirically treated with ceftriaxone and vancomycin. She developed a rash that was attributed to ceftriaxone, which was discontinued. She was continued on her medication regimen with the exception of sulfamethoxazole/trimethoprim. Labs drawn at the medical facility, showed a platelet count of 41,000. On day 2, the patient was diagnosed with drug-induced thrombocytopenia thought to be attributed by divalproex. At that point, divalproex and lamotrigine were discontinued. Over the next few days, her platelet count trended up after discontinuation. On day 4, platelet count was 56,000. On day 5, platelet count was 82,000. On day 8, her platelet count normalized at 368,000. No source of infection was identified and the patient returned to the psychiatric facility on day 8.

Both sulfamethoxazole/trimethoprim and divalproex have case reports of drug-induced thrombocytopenia. Sulfamethoxazole/trimethoprim being one of the most common drugs causing DITP (J Thromb Haemost. 2009 Jun; 7(6): 911918). There is also a known drug-drug interaction between valproic acid and

sulfamethoxazole/trimethoprim, which increases the risk of developing thrombocytopenia if used together (Prescriber's Digital Reference). DITP usually occurs after seven days of starting a new medication. When the offending medication is stopped, the platelet count should normalize within 1-10 days. This adverse drug event occurred exactly seven days after the addition of sulfamethoxazole/trimethoprim. Eight days after discontinuing SMZ-TMP, divalproex and lamotrigine, the patient's platelet count was within normal range. Based on the timeline of events, it is plausible that sulfamethoxazole/trimethoprim is the culprit for the patient's thrombocytopenia.

2. 42 year-old AAF admitted to facility due to being a danger to self/others in July 2018. She has a reported history of intellectual disability (IQ 33 per MHMR) along with schizophrenia; she is also legally blind and has difficulty with hearing. Upon admission, she was displaying signs of psychosis and reported thoughts of suicide. Prior to admission, she was taking risperidone 4mg BID along with benztropine 0.5mg BID and was adherent per reports from family/community caregiver. However, due to the team being uncertain whether or not she had the capacity to consent to medications (pt has no guardian), a court ordered medication petition was filed. In order to prevent withdrawal symptoms from medications, namely withdrawal dyskinesia from antipsychotics, risperidone was continued via STAT orders at the same dosage (4mg twice daily). On day four of her hospitalization, she presented with "little speech, thought blocking, psychomotor retardation" and was "standing in an unnatural position leaning over the back of a chair" per documentation from the treating provider. She also moved very slowly and was noted to have some muscle rigidity in upper extremities bilaterally on exam. Due to suspicion of catatonia and/or EPS, STAT lorazepam and benztropine were administered PO, CK and troponin labs were ordered. After administration of the PO medications, there was reportedly noticeable improvement in her ability to communicate and psychomotor retardation. Around that time, her BP was 138/88, T 97.2, HR 99, RR 18, O2 Sat 96%. The evening shift of nurses were instructed "not to seek STAT Risperdal order" for that night due to strong suspicion of catatonia. Later that evening, labs returned with elevated CK of 18363 U/L (reference range 26-192 U/L), troponin WNL. Admission labs showed normal CMP, including renal function, except for slightly elevated AST 43 U/L (ref range 10-42 U/L), normal TSH, nonreactive RPR, CBC and iron panel indicating iron deficiency anemia. No urine analysis on file. The fourth evening of her hospitalization her vitals were as follows: BP was 148/79 (slightly elevated), T 97.9, HR 84, RR 19, O2Sat 100%. Per a later note by on call physician, HR was apparently elevated at 105 at some point. She was alert and oriented to self only and unable to give her birth date year/age, she continued to display psychomotor retardation which was reportedly worse than the day before per staff. She had been refusing most of her meals and it was unclear if she had been urinating normally.

The on call physician sent her to the medical hospital due to concerns for rhabdomyolysis. While at the medical facility, CK reached levels of at least 2569

IU/L by day 4 at the medical facility and she was treated with IV fluids. CK began to trend downwards. It was unclear exactly when she received these antipsychotic doses, but she was given at least one dose of risperidone 4mg and haloperidol while at the medical hospital, and CK continued to trend downward. When her CK reached a level less than 1000 (913 IU/L on day 6), she was accepted back to our facility. While in the medical hospital, she did not have other typical signs of neuroleptic malignant syndrome (NMS) such as significantly elevated temperature or lead pipe rigidity, so the medical providers and psychiatric providers determined that NMS was not likely. However, due to a low grade fever while hospitalized, tachycardia, and muscle rigidity, the psychiatric provider felt that it was possible that she was having early symptoms of NMS. Risperidone was ordered at a lower dose of 1mg BID and CK/CMPs were ordered twice weekly (Mon and Thursday) to follow up. However, before the first dose of the new risperidone order was administered, the CK level came back at 1267 IU/L (day 10 of hospital stay at our facility), which is increased from the 913 IU/L reported at medical facility. Risperidone was discontinued and daily weekday CKs were ordered: CK was 1132 IU/L on day 15, CK was 1009 IU/L on day 16, which is trending downward but still higher than that at the medical facility level of 913 IU/L. By day 17, CK was down to 662 IU/L. CPK Monitoring continued on a daily basis for the next two weeks, without significant spikes in CPK levels and during that time the patient remained free of antipsychotic treatment. Later CPK monitoring reduced to 3 times a week and patient was initiated on quetiapine and medication titrated slowly. During that time, her CPK did not exceed 610, and her most recent level on day 71 is 290.

CPK elevations with antipsychotic medications is possible but rare in the absence of NMS. The patient's presentation suggests significant elevations in CPK are attributed to risperidone as noted by the fact that her levels dropped soon after discontinuation of the medication and use of IV fluids. Upon giving one dose of risperidone, her CPK trended up again, but nowhere near what it was when a hospital transfer was needed. During the two-week period of being antipsychotic free, no further elevations in CPK were noted, rather levels seemed to hover between 300 and 700s. There is one published case report about a patient who developed elevated CK ad was diagnosed with rhabdomyolysis soon after risperidone was used and titrated, however in that patient, he was also on aripiprazole, which has a long half-life which could have increased the risk of this adverse event. (Journal of Clinical pharmacology: 37(1); 2017). Our patient was only receiving one antipsychotic and it would be important to continue to be vigilant to the possible of developing CPK elevation as other antipsychotics are trialed.

New Drug Applications

1. Linaclotide (Linzess®)- presented by Dr. Burroughs

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

The committee discussed a comparison of lubiprostone (Amitiza®), the formulary medication used to treat chronic idiopathic constipation and irritable bowel syndrome, and linaclotide. The acquisition cost of one lubiprostone soft gel cap is less than half that of a linaclotide capsule. However, lubiprostone is dosed twice daily whereas linaclotide is dosed once daily. Linaclotide capsules can be opened and the contents removed, allowing some flexibility with administration.

On a motion of Dr. Pittman, seconded by Dr. Messer, it was recommended to add linaclotide to the formulary as a reserve agent for patients who are receiving enteral nutrition or who require a modified diet texture. The formulary check List was completed and no issues were detected.

2. Levocarnitine (Carnitor®) - presented by Melanie Chang

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

The committee discussed the use of levocarnitine versus the use of lactulose in reducing ammonia levels caused by treatment with valproic acid.

On a motion of Dr. Messer, seconded by Mr. Dunlap, it was recommended to add levocarnitine to the formulary. The formulary check List was completed and no issues were detected.

3. Fosfomycin (Monurol®)- presented by Dr. Mican

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

The committee discussed the CDC recommendations for the empiric treatment of urinary tract infections: sulfamethoxazole/triamterene, nitrofurantoin, and fosfomycin. Sulfamethoxazole/triamterene is not recommended for use when resistant rates rise above 20%, however not all of the community centers have easy access to culture and sensitivity data. Fosfomycin is more expensive than sulfamethoxazole/triamterene or nitrofurantoin but has the advantage being a one-dose treatment.

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

4. Losartan (Cozaar®)- pending

The request to consider the addition of losartan to the formulary is being tabled until the next meeting when Dr. Heidel will present a monograph.

5. Aripiprazole lauroxil (Initio®)- pending

The request to consider the addition of aripiprazole to the formulary is being tabled due to insufficient time to develop a monograph.

Shingrix® Review

Shingrix® was added to the formulary at the February 2, 2018 EFC meeting. At that time, Shingrix® had been on the market for less than 6 months. When recently marketed drugs are added to the formulary, medication errors and adverse drug events involving the newly added drug are reviewed one year later. No reports of adverse drug events or medication errors involving Shingrix® have been received from the field.

Hepatitis C Drug Purchases

For the first quarter of fiscal year 2019 (September-November 2018), the following purchases for drugs to treat hepatitis C were made:

State Hospitals: $79,508.21

State Supported Living Centers: none

It was noted that individuals in the SSLCs that have Medicare Part D have their drug treatment for hepatitis C obtained from an outside pharmacy. Otherwise, the facility will purchase the drug. The committee will continue to monitor these purchases.

Quarterly Non-Formulary Drug Justification Report

For the first quarter of fiscal year 2019, only the State Hospitals reported use of non-formulary agents. The SSLC facilities currently do not have the reporting capabilities to obtain the non-formulary drugs from their computer system but are working with the vendor to create a report. The following were the top non-formulary agents, by number of orders, that were prescribed in the State Hospitals:

clotrimazole/betamethasone cream (Lotrisone®)
losartan (Cozarr®)
apixiban (Eliquis®)
dexmethylphenidate (Focalin®) note: the ER formulation was added to the formulary at the October 2018 committee meeting.

Drug Deletions

The committee did not consider deleting any additional products not already specified in the sectional review.

New Dosage Strengths

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 infectious disease agents, antineoplastic agents, nutritional agents/nutritional supplements, dementia agents, miscellaneous

CNS agents, and agents for migraine, Dr. Hall made the following recommendations:

1. Infectious Disease
    a) ampicillin
        - delete "capsule, as anhydrous, oral"
        - delete "…as trihydrate," from capsule and powder listings
    b) penicillin injections
        - delete penicillin G benzathine-penicillin G procaine
        - delete penicillin G procaine
        - delete penicillin G sodium
    c) cefuroxime axetil
        - delete powder for suspension, oral listing (discontinued)
    d) miscellaneous antibiotics
        - delete cycloserine from this category, leaving it in the Antituberculars listing
2. Nutritional Agents
    a) Vitamins
        - delete vitamin K from this category, leaving it in the Antidotes and Anticoagulant Agents listings
    b) Minerals, Trace Elements, and Electrolytes
        - delete calcium glubionate
        - delete calcium gluconate

On a motion of Dr. Messer, seconded by Mr. Dunlap, the changes recommended above were approved and the formulary will be updated.

Psychotropic Consent List- annual review

The Psychotropic Consent List was reviewed. The following changes were recommended:

- Add nonformulary status to: maprotiline (Ludiomil®), protriptyline (Vivactil®), trimipramine (Surmonyil®), and nadolol (Corgard®)
- Add ketamine to antidepressant list with Reserve status
- Add midazolam (Versed®) to anxiolytics/sedatives/hypnotics list
- Add buprenorphine (Subutex®) and buprenorphine/naloxone (Suboxone®) to Chemical Dependency Adjunct list with Reserve status
- Add topiramate (Topamax®) to Mood Stabilizers list
- Add Reserve status to lisdexamfetamine (Vyvanse®)
- Add dexmethylphenidate XR (Focalin XR®) as a separate entry on the Stimulants list, as it is formulary and regular dexmethylphenidate (Focalin®) is not.

On a motion of Dr. Bennett, seconded by Dr. Messer, the Psychotropic Consent List was approved with the recommendations listed above. An updated list will be posted to the EFC website.

Formulary Reserve Drug Table- annual review

The Reserve Drugs table was reviewed. Linaclotide was added to the drug formulary in the reserve category (see New Drug Applications).

On a motion of Dr. Sawhey, seconded by Dr. Messer, the above change to the Reserve Drug table was approved.

Formulary Psychotropic Dosing Tables- annual review

The dosing tables were reviewed. The tables will be updated when the final draft of the *Psychotropic Medication Utilization Parameters for Children and Youth in Texas Public Behavioral Health* has been approved by the committee. Dr. Baemayr reported that a similar workgroup will be created to review adult dosing parameters.

On a motion of Dr. Messer, seconded by Dr. Baemayr, the formulary psychotropic dosing tables were approved without change at this time.

Texas Health and Human Services Health and Specialty Care System 2019 Drug Formulary- annual review

The 2019 HHSC Health and Specialty Care System Drug Formulary was presented to Committee. The 2019 formulary will include the changes made during this meeting.

On a motion of Dr. Pittman, seconded by Dr. Messer, the Texas Health and Human Services Health and Specialty Care System 2019 Drug Formulary was approved. The updated Formulary will be posted to the EFC website.

USP <800>

The committee reviewed two documents:

- *NIOSH List of Antineoplastics and Other Hazardous Drugs in Healthcare Settings 2016.*

The National Institute for Occupational Safety and Health (NIOSH) list includes drugs that are considered hazardous because they exhibit at least one of the following:

- Carcinogenicity
- Teratogenicity or other developmental toxicity
- Reproductive toxicity
- Organ toxicity at low doses
- Genotoxicity
- Structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the above criteria

Included on the NIIOSH list are several drugs commonly used by the Health and Specialty Care System, including clonazepam, divalproex/valproic acid,

oxcarbazepine, paliperidone, paroxetine, phenytoin, and risperidone. The NIOSH list includes recommendations for personal protective equipment (PPE) to be used when handling hazardous drugs.

- *USP General chapter <800> Hazardous Drugs-Handling in Healthcare Settings*

USP General Chapter 800 describes practice standards for the handling of hazardous drugs. These standards will become official on December 1, 2019. USP 800 adopts the drugs identified on the NIOSH list, as well as the PPE recommendations. Alternative containment strategies may be used if a facility performs an assessment of risk. A workgroup is currently working on developing policy and procedures and training, as well as identifying appropriate equipment and supplies. Dr. Pittman noted that the SSLC's will are not planning on implementing the USP 800 standards.

Issues from the Medical Director, State Hospital System

Dr. Muse was not present at this point of the meeting and did not provide any information to report.

Issues from the Medical Director, State Supported Living Centers

Dr. Taylor and Dr. Shipley had no issues to report to the committee.

FDA Drug Safety Communications

The FDA has issued the following safety communication that may impact our facilities.

Phenytoin (Dilantin):

Additions and/or revisions are underlined:

Cases of bradycardia and cardiac arrest have been reported in DILANTIN-treated patients, both at recommended phenytoin doses and levels, and in association with phenytoin toxicity. Most of the reports of cardiac arrest occurred in patients with underlying cardiac disease.

Metformin:

Additions and/or revisions underlined:

Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Measure hematologic parameters on an annual basis and vitamin B12 at 2 to 3 year intervals.

In clinical trials of 29-week duration with metformin HCl tablets, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients

Lacosamide (Vimpat):

Additions and/or revisions underlined:

Vimpat should be used with caution in patients with underlying proarrhythmic conditions such as known cardiac conduction problems (e.g., marked first-degree AV block, second-degree or higher AV block and sick sinus syndrome without pacemaker), severe cardiac disease (such as myocardial ischemia or heart failure, or structural heart disease), and cardiac sodium channelopathies (e.g., Brugada Syndrome). VIMPAT should also be used with caution in patients on concomitant medications that affect cardiac conduction, including sodium channel blockers, beta-blockers, calcium channel blockers, potassium channel blockers, and medications that prolong the PR interval. In such patients, obtaining an ECG before beginning VIMPAT, and after VIMPAT is titrated to steady-state maintenance dose, is recommended.

Cariprazine (Vraylar):

Additions and/or revisions underlined:

… There are no available data on VRAYLAR use in pregnant women to inform any drug-associated risks for birth defects or miscarriage. The major active metabolite of cariprazine, DDCAR, has been detected in adult patients up to 12 weeks after discontinuation of VRAYLAR.

Quetiapine (Seroquel):

Addition of the following:

Agranulocytosis (defined as absolute neutrophil count <500/mm3) has been reported with quetiapine, including fatal cases and cases in patients without pre-existing risk factors. Neutropenia should be considered in patients presenting with infection, particularly in the absence of obvious predisposing factor(s), or in patients with unexplained fever, and should be managed as clinically appropriate.

Aripiprazole lauroxil (Aristada):

Newly added subsection:

Medication errors, including substitution and dispensing errors, between ARISTADA and ARISTADA INITIO could occur. ARISTADA INITIO is for single administration in contrast to ARISTADA which is administered monthly, every 6 weeks, or every 8 weeks. Do not substitute ARISTADA INITIO for ARISTADA because of differing pharmacokinetic profiles.

Lithium:

Additions and/or revisions are underline:)

Neurological signs of lithium toxicity range from mild neurological adverse reactions such as fine tremor, lightheadedness, lack of coordination, and weakness; to moderate manifestations like giddiness, apathy, drowsiness, hyperreflexia, muscle twitching, ataxia, blurred vision, tinnitus, and slurred speech; and severe manifestations such as clonus, confusion, seizure, coma, and death. In rare cases, neurological sequelae may persist despite discontinuing lithium treatment and may be associated with cerebellar atrophy.

FDA Drug Recalls

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

Irbesartan (Avapro®)

Aurobindo Pharma Limited is voluntarily recalling 22 batches of irbesartan due to the presence of an impurity, N-nitrosodiethylamine (NDEA). The irbesartan drug substance was supplied to ScieGen Pharmaceuticals Inc., U.S. for the manufacturing of finished irbesartan drug product, subsequently labeled as Westminster Pharmaceuticals and Golden State Medical Supply.

Losartan-Hydrochlorothiazide

Sandoz Inc. is voluntarily recalling one lot of losartan-hydrochlorothiazide (HCTZ) tablets, 100mg/25mg to the consumer level due to the trace amount NDEA contained in the active pharmaceutical ingredient (API) losartan, manufactured by Zhejiang Huahai Pharmaceutical. Sandoz losartan-hydrochlorothiazide product is manufactured by Lek Pharmaceuticals in Ljubljana, Slovenia.

Losartan (Cozaar®)

Torrent Pharmaceuticals Limited is expanding its voluntary recall from 2 lots of losartan potassium tablets USP to a total of 10 lots, to the consumer level due to the detection of trace amounts of NDEA found in an API manufactured by Hetero Labs Limited. Torrent is only recalling lots of losartan-containing products that contain NDEA above the acceptable daily intake levels released by the FDA.

Valsartan (Diovan®), valsartan-hydrochlorothiazide, valsartan-amlodipine, valsartan-hydrochlorothiazide-amlodipine

-Mylan Pharmaceuticals is conducting a voluntary recall to the consumer level of all lots of valsartan-containing products due to detected trace amounts of NDEA.

-Teva Pharmaceuticals has initiated a voluntary recall, to the patient level, of all lots of amlodipine-valsartan combination tablets and amlodipine-valsartan-HCTZ tablets due to NDEA found in the API manufactured by Mylan India.

-Aurobindo Pharma USA, Inc. is conducting a voluntary recall of 80 lots of amlodipine-valsartan tablets, valsartan-HCTZ Tablets, and valsartan tablets to the consumer level due to the detection of trace amounts of NDEA. To date, Aurobindo Pharma USA, Inc. has not received any reports of adverse events related to this recall.

Sodium chloride for injection

Fresenius Kabi USA is voluntarily recalling 163 lots of Sodium Chloride Injection, 0.9%, 10 mL vials and 20 mL vials to the user level. The product insert states that stoppers for both the 10mL and the 20mL vials do not contain natural rubber latex; the tray label for the two vial sizes and the vial label for the 20mL vial also state that the stoppers do not contain latex. The product is being recalled because the stoppers contain natural rubber latex.

Ceftriaxone for injection

Lupin Pharmaceuticals, Inc. is voluntarily recalling 5 lots of ceftriaxone injection, 250mg, 10 lots of ceftriaxone injection, 500mg, 24 lots of ceftriaxone injection, 1g and 3 lots of ceftriaxone injection, 2g, to the hospital/physician level. The products have been found to contain visual grey particulate matter in reconstituted vials.

Improper piercing and use of a needle greater than 21 gauge (larger internal diameter), while reconstituting the vial, can push rubber flecks into the solution. There were no grey flecks seen prior to the reconstitution of the vials and the issue was identified upon standard visual inspection prior to patient administration.

If injected, this product (containing rubber particulate matter from the stopper) could cause vein irritation/phlebitis or pulmonary embolic events that could result in permanent impairment of body function or damage to body structures, such as the lungs and vascular system. In addition, as ceftriaxone can be administered intramuscularly, the use of the product may result in local muscle inflammation and/or abscesses.

News Briefs

The following information was shared with the committee members:

CNN (11/1, Tinker) reports Epidiolex, the first FDA-approved cannabis-based medication, is now available by prescription across the country. The drug is "approved for use in patients 2 and older to treat two types of epileptic syndromes: Dravet syndrome, a rare genetic dysfunction of the brain that begins in the first year of life, and Lennox-Gastaut syndrome, a form of epilepsy with multiple types of seizures that begins in early childhood, usually between ages 3 and 5." **The Atlanta Journal-Constitution (11/1, Pirani)** reports the "average list price of Epidiolex is $32,500 annually.

Reuters (11/2, Joseph) reported an advisory panel to the FDA on Friday recommended approval of Sage Therapeutic's experimental treatment for postpartum depression Zulresso (brexanolone). FDA staff reviewers had "raised safety concerns over the loss of consciousness in certain patients who were on the treatment." Due to side effects, the panel recommended a "monitoring period after women receive the injection" and "against home use of the drug." The FDA has until December 19 to decide whether to follow the recommendation of the Psychopharmacologic Drugs Advisory Committee.

USA Today (11/14, Alltucker) reported that following the recall of valsartan, irbesartan, and losartan, FDA Commissioner Dr. Scott Gottlieb said the FDA has recruited "dozens of chemists to review pharmaceutical companies and monitor for any changes in manufacturing techniques" to help "prevent drug impurities that may be harmful to consumers."

Fierce Pharma (11/28) reports the FDA approved a six-month exclusivity extension for Pfizer's Lyrica (pregabalin). According to Fierce Pharma, the drug's "patent shield was set to expire at the end of the year, but its protections will now

run through June 30, 2019. Last year, Lyrica pulled in nearly $3.5 billion in the U.S., and the patent extension should allow Pfizer to protect about half of that figure next year."

Open Forum

No items.

Next Meeting Date

The next meeting was scheduled for April 5, 2019.

Adjourn

There being no further business, the meeting was adjourned at 2:08 p.m.

Approved: *Mark Messer, D.O.*

Mark Messer, D.O., Chairman

Minutes Prepared by:

Jean Baemayr, PharmD

Appendix

Appendix A – linaclotide New Drug Application and monograph
Appendix B – levocarnitine New Drug Application and monograph
Appendix C – fosfomycin New Drug Application and monograph

APPENDIX 1: NEW DRUG APPLICATION FORM

415-C
EXHIBIT A

TEXAS HHS STATE HOSPITAL SYSTEM
NEW DRUG APPLICATION
(for inclusion in the Texas HHS *Drug Formulary*)

(The new drug application process is described on the back of this form)

Date: 8/31/18

Name of practicitioner submitting the application: Ashton Wickramasinghe MD
Christie, Pharm D and

Name of entity with which the practictioner 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)):
Austin State Hospital Luvy Center

Information regarding the new drug:

Therapeutic Classification	GI drug; miscellaneous
Generic Name	Linaclotide
Trade Name(s)	Linzess
Manufacturer(s)	Ironwood pharmaceuticals
Dosage Form(s)	145mcg and 290mcg capsules

Explain the pharmacological action or use of this drug:
Guanylate Cyclase-C (GC-C) agonist. Used for idiopathic and IBS constipation

Explain the advantages of this drug over those listed in the formulary:
Capsules can be opened for administration to patients on g-tube or required

State which drugs this new drug would replace or supplement: Constipation meds
Amitiza

☐ Application is approved

OR

☐ Application is appropriate and complete

Signature of chairman of facility pharmacy and therapeutics committee

Signature of medical director or designee

Linaclotide (Linzess®)

Classification:

Gastrointestinal Agent—Guanylate Cyclase-C (GC-C) Agonist

Pharmacology:

Mechanism of Action: Linaclotide is structurally related to human guanylin and uroguanylin and functions as a guanylate cyclase-C agonist. Both linaclotide and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation in intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel, resulting in increased intestinal fluid and accelerated transit. {1,8}

Pharmacokinetics:

Absorption:

Linaclotide is minimally absorbed with negligible systemic availability following oral
administration.

Distribution:

Given that linaclotide plasma concentrations following recommended oral doses
are not measurable, linaclotide is not expected to be distributed to tissues to any clinically relevant extent.

Metabolism:

Linaclotide is metabolized within the gastrointestinal tract to its principal, active metabolite by loss of the terminal tyrosine moiety. Both linaclotide and the metabolite are proteolytically degraded within the intestinal lumen to smaller peptides and naturally occurring amino acids.

Excretion:

Active peptide recovery in the stool samples of fed and fasted healthy subjects
following administration of linaclotide 290 mcg once daily for seven days averaged
about 5% (fasted) and 3% (fed) and all of it as the active metabolite. {1}

Indications:

Chronic idiopathic constipation in adults
Irritable bowel syndrome with constipation {2}

Dosage and administration:

Administer orally at least 30 minutes before the first meal of the day on an empty stomach.
Capsules should not be broken, crushed or chewed. For patients with swallowing difficulties, capsules can be opened and administered orally either in applesauce or with water. For patients
with a nasogastric or gastric feeding tube, capsules can be opened and sprinkled into 30 mL of room temperature bottled water and administered per tube. Dosage for chronic idiopathic constipation is 145 mcg once daily. A dosage of 72 mcg once daily may be used based on individual presentation or tolerability. Dosage for irritable bowel syndrome with constipation is 290 mcg once daily. {1,2}.

Contraindications:

- Patients less than 6 years of age due to the risk of serious dehydration.
- Patients with known or suspected mechanical gastrointestinal obstruction.

Precautions:

- Risk of serious dehydration in pediatric patients.
- Diarrhea

Adverse Reactions:

- The most common adverse reactions in patients with IBS-C were diarrhea, abdominal pain, flatulence, abdominal distension, viral gastroenteritis and headache.
- The most common adverse reactions with CIC were diarrhea, abdominal pain, flatulence, abdominal distension, upper respiratory infection and sinusitis.

Interactions:

- No known significant reactions.

Monitoring:

- CIC-Frequency of straining during bowel movements; spontaneous bowel movement quality and frequency.
- IBS-C-Abdominal pain, spontaneous bowel movement quality and frequency.

HHSC Cost:

Acquisition cost comparison of GC-C agonists available to HHSC facilities.

Linaclotide 145 mcg--$13.18 Linaclotide 290 mcg—$13.18 Linaclotide 72 mcg--$14.13

Price comparison: Plecanatide 3mg--$13.73

Both are once daily dosing.

Efficacy:

The efficacy of linaclotide in the treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) was established in multiple randomized, multicenter,

double-blind, parallel-group, placebo-controlled, dual-dose trials. {3,4,5,6,7}

Conclusion:

Linaclotide has been evaluated in a large clinical trial program both for chronic constipation (dose of 145 mcg) and constipation-predominant irritable bowel syndrome (dose of 290 mcg) demonstrating significant and clinically relevant efficacy in improving both broad variety of constipation symptoms as well as abdominal pain and bloating. Diarrhea has been determined as the only relevant adverse effect causing treatment cessation. Linaclotide is one of two guanylate cyclase-C receptor agonists which can be considered after first-line therapies are all exhausted in a stepwise approach for IBS-C and CIC for the patients in our facility. It would be favorable to add linaclotide to our formulary.

References:

1. Product Information: Linzess® capsules. Allergan and Inwood Pharmaceuticals, Inc. Irvine, CA; Cambridge, MA. 2017.
2. Linaclotide Monograph. Lexi-Drugs. Lexi-comp online. Wolters-Kluwer. Accessed 12/27/2018.
3. Alammar, N and Stein, E. Irritable Bowel Syndrome: What Treatments Really Work. Med Clin N Am 103 (2019) 137-152.

4. Lembo, A, Scheier, H et al. Two Randomized Trials of Linaclotide for Chronic Constipation. N Engl J Med 365:6 NEJM.ORG 527-536: 2011.
5. Chey, W, Lembo et al., Linaclotide for Irritable Bowel Syndrome with Constipation: A 26 week, Randomized, Double-blind, Placebo-controlled Trial to Evaluate Efficacy and Safety. www.amjgastro.com The American Journal of Gastroenterology. Vol. 107, 1702-1712. 2012.
6. Johnston, J, Kurtz, c et al. Pilot Study on the Effect of Linaclotide in Patients with Chronic Constipation. The American Journal of Gastroenterology. 125-132. 2009.
7. Rao, S, Lembo, A et.al. A 12 week Randomized Controlled Trial with a 4-week Randomized Withdrawal Period to Evaluate the Efficacy and Safety of Linaclotide in Irritable Bowel Syndrome with Constipation. www.amjgastro.com . 2012.
8. www.Uptodate.com Management of chronic constipation in adults. Accessed 01/07/2019.
9. Andresen, V Medical Therapy of Constipation: Current Standards and Beyond. Visceral Medicine 2018;34:123-127.

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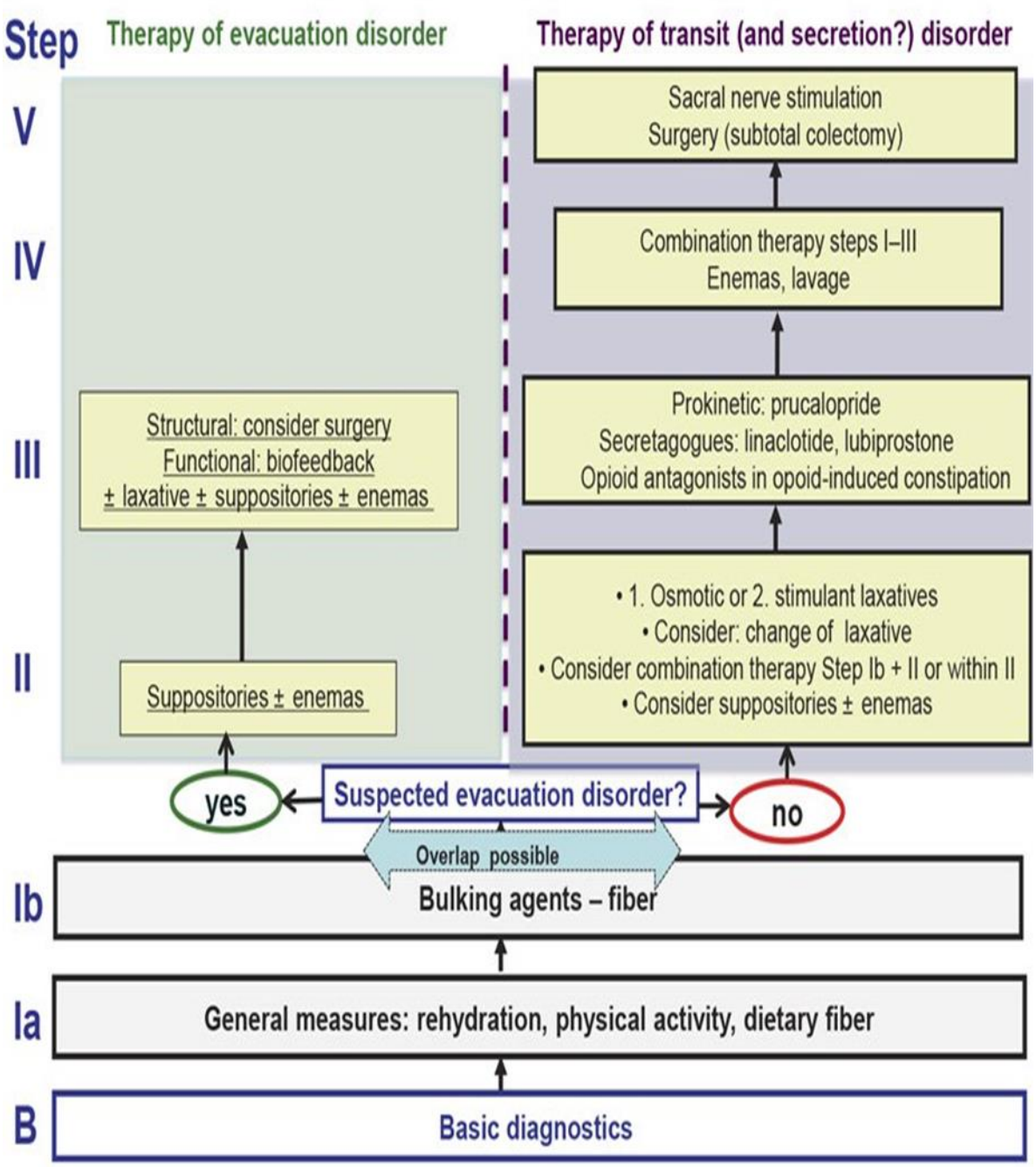
Abilene State Supported Living Center


Step
Therapy of evacuation disorder
Therapy of transit (and secretion?) disorder
V
Sacral nerve stimulation
Surgery (subtotal colectomy)
IV
Combination therapy steps I–III
Enemas, lavage
III
Structural: consider surgery
Functional: biofeedback
± laxative ± suppositories ± enemas
Prokinetic: prucalopride
Secretagogues: linaclotide, lubiprostone
Opioid antagonists in opoid-induced constipation
II
Suppositories ± enemas
• 1. Osmotic or 2. stimulant laxatives
• Consider: change of laxative
• Consider combination therapy Step Ib + II or within II
• Consider suppositories ± enemas
yes
Suspected evacuation disorder?
no
Overlap possible
Ib
Bulking agents – fiber
Ia
General measures: rehydration, physical activity, dietary fiber
B
Basic diagnostics

APPENDIX 1: NEW DRUG APPLICATION FORM

TEXAS DEPARTMENT OF MENTAL HEALTH AND MENTAL RETARDATION

NEW DRUG APPLICATION

(for inclusion in the *DSHS/DADS Drug Formulary*)

** (THE NEW DRUG APPLICATION PROCESS IS DESCRIBED ON THE BACK OF THIS FORM.) **

Date: 9-20-18

Name of practitioner submitting the application: Lisa Mican

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

Information regarding new drug:

Therapeutic Classification	Amino Acid Supplement
Generic Name	L-carnitine, levocarnitine
Trade Name(s)	Carnitor
Manufacturer(s)	Leadiant Bio Inc,
Dosage Form(s)	tablet, solution

Explain the pharmacological action or use of this drug: Supplement, ↓ ammonia

Explain the advantages of this drug over those listed in the formulary: effective for ↑ ammonia 2o VPA & can be use for those with intolerance of lactulose, carnitine deficiency

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

****

☑ application is approved — 9/20/18
signature of chairman of facility pharmacy and therapeutics committee

OR

☐ application is appropriate and complete
signature of clinical/medical director or designee

Levocarnitine (Carnitor®)

Classification: Dietary supplement

Pharmacology:

- Mechanism of action: Carnitine is a naturally occurring metabolic compound which functions as a carrier molecule for long-chain fatty acids within the mitochondria, facilitating energy production. Carnitine deficiency is associated with accumulation of excess acyl CoA esters and disruption of intermediary metabolism, which may lead to a buildup of excess organic or fatty acids in patients with defects in fatty acid metabolism.[1,2]

Pharmacokinetics:

- Absorption: Following 4 days of dosing 1980 mg of Carnitor® tablets BID or 2 g of Carnitor® oral solution BID, the maximum plasma concentration was about 80 µmol/L and the time to maximum plasma concentration occurred at 3.3 hours. The absolute bioavailability of levocarnitine, calculated after correction for circulating endogenous plasma concentrations of levocarnitine, was 15.1 $\pm$ 5.3% for Carnitor® Tablets and 15.9 $\pm$ 4.9% for Carnitor® Oral Solution.[1]
- Distribution: V_d ~ 29 L (0.39 L/kg). The plasma concentration profiles of levocarnitine after a slow 3-minute intravenous bolus dose of 20 mg/kg of Carnitor® were described by a two-compartment model. Using plasma concentrations uncorrected for endogenous levocarnitine, the mean distribution half-life was 0.585 hours.[1]
- Metabolism: In a pharmacokinetic study where five normal adult male volunteers received an oral dose of [^{3}H-methyl]-L-carnitine following 15 days of a high carnitine diet and additional carnitine supplement, 58 to 65% of the administered radioactive dose was recovered in the urine and feces in 5 to 11 days. Major metabolites found were trimethylamine N-oxide, primarily in urine (8% to 49% of the administered dose) and [^{3}H]-γ-butyrobetaine, primarily in feces (0.44% to 45% of the administered dose).[1]
- Elimination: Following a single IV administration, approximately 76% of the levocarnitine dose was excreted in the urine during the 0-24h interval, 4% to 8% as unchanged drug. The mean apparent terminal elimination half-life was 17.4 hours. Total body clearance of levocarnitine (Dose/AUC including endogenous baseline concentrations) was a mean of 4.00 L/h.[1]

Indications:

- Carnitine deficiency (primary or secondary)
- Carnitine deficiency in patients with ESRD requiring dialysis [injection only]
- Valproic acid induce hyperammonemia (off-label use)

Dosage:

- Carnitine deficiency (primary or secondary): Oral:
    - Tablet: Initial: 990 mg two to three times a day, depending on clinical response.

    - Oral solution: Initial: 1,000 mg/day in divided doses (every 3 to 4 hours); titrate slowly as needed up to 3,000 mg/day in divided doses based on tolerance and therapeutic response; higher doses may be needed in some patients (administer with caution).
- Carnitine deficiency (secondary): IV: 50 mg/kg/day in divided doses (every 3 to 4 hours, no less than every 6 hours). Doses may go up to 300 mg/kg/day (maximum reported). In patients with severe metabolic crisis, a 50 mg/kg loading dose followed by an additional 50 mg/kg over the next 24 hours in divided doses may be required.
- Valproic acid hyperammonemia: 1980-2500mg divided twice daily per published case reports

Administration:

- Carnitor® Tablets and Carnitor® Oral Solution are for oral use only. Not for parenteral use.

Storage:

- Carnitor® Tablets and Carnitor® Oral Solution are stored at controlled room temperature (25°C).

Contraindications:

- No contraindications known according to the manufacturer's labeling.

Precautions:

- Gastrointestinal effects: Gastrointestinal reactions may occur from rapid consumption of oral carnitine; evenly space doses throughout the day and consume slowly to maximize tolerance.
- Hypersensitivity reactions: Serious hypersensitivity reactions have been reported after oral and IV administration. Reactions to oral levocarnitine include rash, urticaria, and facial edema. Reactions to IV administration were primarily seen in patients with ESRD and included anaphylaxis, laryngeal edema and bronchospasms. Levocarnitine should be discontinued if hypersensitivity suspected and medical attention should be sought.

Interactions:

- Warfarin: INR increase has been reported when levocarnitine is taken comncurrently with warfarin. Frequent INR monitoring advised upon initiation and dose adjustment of levocarnitine.
- There are no known CYP450 interactions.

Adverse Reactions:

- Mild gastrointestinal complaints have been reported during long-term use of levocarnitine, including nausea, vomiting, diarrhea, and abdominal cramps. Seizures have been reported in patients with or without pre-existing seizure history though an increase in seizure frequency and/or severity has been reported in patients with pre-existing seizure activity. Other known adverse effects include mild myasthenia in uremic patients and drug-related body odor. Decreasing the dosage often diminishes or eliminates body odor or gastrointestinal symptoms when present.

Use in Special Populations:

- Renal impairment: The safety and efficacy of oral levocarnitine has not been evaluated in patients with renal insufficiency. Long-term administration of oral levocarnitine in patients with severe renal insufficiency or ESRD on dialysis may result in accumulation of toxic metabolites.
- Hepatic impairment: no dose adjustment provided in manufacturer's labeling.
- Pregnancy: Pregnancy Category B: No adverse effects or evidence of impaired fertility or harm to fetus during animal studies. There are no adequate and well controlled studies in pregnant women.
- Lactation: Animal studies show increase in levocarnitine concentration in milk following its administration. There are no studies specifically looking at levocarnitine supplementation in nursing human mothers.

Cost Comparisons:

Name	Strength (mg)	Manufacturer	Unit Cost-per tablet ($)
Carnitor	330	SIG	0.983
Levocarnitine	330	AKR	0.779
Levocarnitine	500	N-B	0.309 (average)

Monitoring:

- Periodic blood chemistry (CMP and CBC)
- Vital signs
- Plasma carnitine concentrations
- Overall clinical condition

Efficacy:

- A retrospective cohort study evaluated the overall incidence and treatment management of VPA-induced hyperammonemia in 347 adult patients admitted to the psychiatric unit at a community teaching hospital.[3] The study's primary outcome was the prevalence of hyperammonemia in these patients. The secondary outcomes looked at the prevalence of symptomatic hyperammonemia and the prevalence and efficacy of treatments for hyperammonemia. The choices for treatment included discontinuation of VPA, VPA dose reduction, lactulose, levocarnitine, or a combination of lactulose and levocarnitine. The standard dosing for lactulose was 20 g to 30 g three to four times daily, and the standard dosing for levocarnitine was 300 mg three times daily. Treatment success was defined as achieving an ammonia level of less than 47 μmol/L at discharge (or the most recent ammonia level if one was not drawn on the day of discharge). Decreases between the initial and final ammonia levels were also calculated, as percentages of the initial level. All patients had received at least one dose of VPA or divalproex sodium during admission and had at least one ammonia level drawn during admission. Patients were excluded if they had a diagnosis of cirrhosis. Of the 347 patients screened for hyperammonemia, 125 patients

had ammonia levels considered to be above the upper limit of normal (47 µmol/L, according to hospital protocol), and 113 of these patients were analyzed for the secondary treatment outcome. Discontinuation of VPA was shown to be the most successful (18/32, 56.3%), with levocarnitine therapy being the next most successful (19/38, 50.0%). However, the differences in success rates were statistically insignificant between all treatments overall (P=0.30). VPA discontinuation showed a mean percentage ammonia decrease of 27.4% compared to 8.9% if not discontinued (P=0.07), while levocarnitine showed a mean percentage ammonia decrease of 12.3% compared to 14.8% with other treatments or no treatment (P=0.73). There was not a significant difference in ammonia-level changes between patients treated with levocarnitine and untreated patients (P=0.09).

- A case series and literature review looked at a total of nine cases (three from chart review, six from a literature search) that utilized levocarnitine in VPA-treated patients with psychiatric disorders that had developed hyperammonemia[4]. Case 1 involved a 65-year old male with bipolar I disorder that was admitted for an acute manic episode. After being titrated up to 3,000 mg/day of valproate and 6 mg/day of risperidone, he developed somnolence with garbled speech and altered mental status. Laboratory testing revealed a VPA of 68 µg/mL and an ammonia level of 56 µmol/L. Valproate was discontinued and symptoms resolved. The patient was later started on lithium 900 mg/day and valproate 1,000 mg/day, which was eventually increased to 1,500 mg/day in two divided doses. At the time of the valproate dose increase, the patient was initiated on levocarnitine 990 mg daily and eventually titrated to 990 mg twice daily. Upon recheck, valproate level was 50 µg/mL and ammonia was 23 µmol/L with no symptoms of encephalopathy. Valproate was continued outpatient, but levocarnitine was not renewed (reason unknown). The patient was admitted to the hospital for encephalopathy about 3 months later with an ammonia level of 66 µmol/L and a valproate level of 19 µg/mL (as it was held for somnolence). Valproate was discontinued and not restarted. Case 2 involved a 64-year old male with schizoaffective disorder, bipolar type, whose valproate dosing was at 2,750 mg/day with a valproate trough of 141 µg/mL. An ammonia level was drawn and was 63 µmol/L. One dose of levocarnitine 990 mg was given. Ten hours later, ammonia was decreased to 44 µmol/L. The patient was discharged on levocarnitine 990 mg daily for two days, then 990 mg twice daily. Eventually, the patient was readmitted to the hospital with a valproate level of 70 µg/mL on divalproex ER 2,500 mg/day and an ammonia level of 75 µmol/L. After 9 days of witnessed adherence to levocarnitine 330 mg three times daily, ammonia level decreased to 29 µmol/L. The patient was discharged on levocarnitine 990 mg twice daily to be continued with divalproex. Case 3 involved a 53-year old male with bipolar I disorder in an acute manic episode. Patient was on 2,000 mg/day valproate and ammonia level peaked at 82 µmol/L with valproate at 104 µg/mL.

Lactulose was started for hyperammonemia and given for three days. Two days after lactulose initiation, levocarnitine was also initiated at 1,000 mg daily for three days, then increased to twice daily, and eventually to 1,000 mg every morning and 1,500 mg every evening. Ammonia levels decreased to a range of 46 to 59, and the patient was discharged on valproate and levocarnitine. The patient was eventually readmitted with a valproate level of 115 µg/mL and an ammonia level of 74 µmol/L, which decreased to 30 µmol/L after levocarnitine supplementation.

- A case report followed a 51-year old woman who intentionally ingested a dose of about 60 grams of valproic acid[5]. She presented within 30 minutes of ingestion and her treatment included multiple doses of activated charcoal, levocarnitine and hemodialysis, and required ICU admission with intubation and other supportive measures. The patient was first managed in the ED with 50 g of activated charcoal. At one hour, her VPA level came back at 379.6 µg/mL, and multiple doses of activated charcoal were started at 0.5 g/kg every 4 hours. A loading dose of levocarnitine was also administered at this time (100 mg/kg IV), followed by a maintenance dose of 15 mg/kg every 4 hours. Her VPA level continued to rise until peaking at 905.1 µg/mL about 12 hours after presentation. Continuous renal replacement therapy (CRRT) was planned and started 25 hours after the initial presentation. Eight hours following CRRT, her VPA level was at 417 µg/mL. Hemodialysis was initiated at this point for 8 hours, and the level dropped further to 94 µg/mL. Her ammonia levels were elevated, peaking at 393 mmol/L, but improved with management.

Safety:

- A retrospective, systematic review evaluated the use of intravenous levocarnitine for VHE from retrospective trials and case reports between 1948 and May 2011.[6] There were no reported adverse events in any of the evaluated trials, or in any of the more current trials. An additional systematic review evaluated the incidence of levocarnitine-induced seizures in patients on valproic acid, and found no literature supporting the claim that levocarnitine supplementation may induce seizures in patients on valproic acid.[7] There have been no reports of toxicity from levocarnitine overdose. Levocarnitine is easily removed from plasma by dialysis. The oral LD_{50} of levocarnitine in mice is 19.2 g/kg. High dose levocarnitine may cause side effects such as diarrhea.

Conclusions:

- Data for the efficacy and safety of levocarnitine is minimal, being limited to observational trials and case reports. In the available literature, levocarnitine has been shown to effectively reverse carnitine deficiency, reduce elevated ammonia levels, and improve symptoms of valproate-induced hyperammonemic encephalopathy. Levocarnitine has shown comparable efficacy to lactulose for reducing ammonia levels in patients with VPA-induced hyperammonemia. In addition, levocarnitine has also been shown to

be effective in the prevention of hyperammonemia while on chronic valproate therapy. The adverse effect profile of levocarnitine is minimal, with no reported adverse events occurring in any recent studies, including increased risk of seizures, which was cited on the package insert and drug databases without references. Even at the maximum daily oral dose of 3 g/day, levocarnitine is an inexpensive choice for treatment.

Recommendation:

- Levocarnitine is a cost-effective option for VPA-induced hyperammonemic encephalopathy and for hyperammonemia prevention with chronic valproate therapy. Recommended for formulary approval for both indications.

References:

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2. Lexi-Drugs. Lexicomp [Internet]. Hudson, OH: Wolters Kluwer Health, Inc. 1978-2018. Carnitine supplements (Levocarnitine); [cited 2018 Oct 15]. Available from: http://online.lexi.com.
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5. Al Jawder S, Al Jishi E, Al-Otaibi S, Al-Shahrani MS. All guns blazing: management and survival of massive valproic acid overdose – case report and literature review. Open Access Emergency Medicine: OAEM. 2018;10:31-36. doi:10.2147/OAEM.S151095.
6. Mock CM, Schwetschenau KH. Levocarnitine for valproic-acid-induced hyperammonemic encephalopathy. Am J Health Syst Pharm 2012; 69:35.
7. Zeiler FA, Sader N, Gillman LM, West M. Levocarnitine induced seizures in patients on valproic acid: A negative systematic review. Seizure 2016; 36:36.

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415 — C
EXHIBIT A

APPENDIX 1: NEW DRUG APPLICATION FORM

TEXAS DEPARTMENT OF MENTAL HEALTH AND MENTAL RETARDATION

NEW DRUG APPLICATION

(for inclusion in the *DSHS/DADS Drug Formulary*)

** (THE NEW DRUG APPLICATION PROCESS IS DESCRIBED ON THE BACK OF THIS FORM.) **

Date: 12/6/18

Name of practitioner submitting the application: Lisa Miau

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

Austin State Hospital

Information regarding new drug:

Therapeutic Classification	Antibiotic
Generic Name	fosfomycin tromethamine
Trade Name(s)	Monurol
Manufacturer(s)	Allergan
Dosage Form(s)	oral sachet packet (granules)

Explain the pharmacological action or use of this drug: Bactericidal action due to inactivation of the enzyme enolpyruvyl transferase blocking one of the first steps in material cell wall synthesis

Explain the advantages of this drug over those listed in the formulary:
CDC recommends nitrofurantoin, Bactrim DS or fosfomycin as appropriate 1st line agents for uncomplicated UTI

State which drugs this new drug would replace or supplement:
Sulfamethoxazole/trimethoprim for empiric UTI treatment (uncomplicated) as our resistance rate is too high for empiric use (>20%) would supplement nitrofurantoin

☐ application is approved

OR

☒ application is appropriate and complete

signature of chairman of local pharmacy and therapeutics committee

signature of clinical/medical director or designee: MD

Fosfomycin Tromethamine (Monurol®)

Classification: Antibiotic

Pharmacology:
MONUROL (fosfomycin tromethamine) Granules for Oral Soultion contains fosfomycin tromethamine, a broad spectrum bactericidal antibiotic. Fosfomycin (the active component of fosfomycin thromethamine) has in vitro activity against a broad range of gram-positive and gram-negative aerobic microorganisms which are associate with uncomplicated urinary tract infections. As a phosphonic acid derivative, fosfomycin inhibits bacterial wall synthesis by inactivating the enzyme, enolpyruvyl transferase, which is critical in the synthesis of cell walls by bacteria.[1]

Pharmacokinetics:[1]

Absorption	Following oral administration, fosfomycin tromethamine is rapidly absorbed and converted to the free acid, fosfomycin. After a single 3-gram dose of fosfomycin, the mean maximum serum concentration achieved was 26.1 mcg/mL within 2 hours; with a high-fat meal it was 17.6 mcg/mL within 4 hours.
Distribution	Fosfomycin is distributed to the kidneys, bladder wall, prostate, and seminal vesicles. Fosfomycin is not protein bound. The mean apparent steady-state volume of distribution is 136.1 L.
Elimination	Fosfomycin is excreted unchanged in urine (38%) and feces (18%). Mean half-life elimination is 5.7 hours; CrCl 7-54 mL/min is 50 hours. Urinary excretion decreases to 11% in patients with CrCl 7-54 mL/min.

Indications and Usage:
- Fosfomycin is FDA approved for the treatment of uncomplicated urinary tract infections (acute cystitis) in women due to susceptible strains of *Escherichia coli* and *Enterococcus faecalis*.[1]
- Off-label use in males for uncomplicated urinary tract infections and prostatitis.[2]
- Not indicated for the treatment of pyelonephritis or perinephric abscess.[1]
- If persistence or reappearance of bacteriuria occurs after treatment with fosfomycin, other therapeutic agents should be selected.[1]

Dosage and Administration:
- The FDA approved dosage for females 18 years of age and older for uncomplicated urinary tract infection (acute cystitis) is 3 g (one sachet) of fosfomycin.[1]
- Off-label use in males for complicated urinary tract infection is 3 g every 2 to 3 days for 3 doses orally. The off-label use for prostatitis is 3 g every 3 days for a total of 21 days orally.[2]
- Fosfomycin may be taken with or without food.
- Always mix fosfomycin with 3 to 4 oz (90 to 120 mL) cool water before ingesting. Do not administer in its dry form or mix with hot water.

Contraindications:
Fosfomycin is contraindicated in patients with known hypersensitivity to the drug.[1]

Precautions:[1]

- Prolonged use may result in fungal or bacterial superinfection. *Clostridium difficile* associated diarrhea (CDAD) and pseudomembranous colitis has been reported with use of nearly all antibacterial agents, including fosfomycin, and may range in severity from mild diarrhea to fatal colitis. Therefore, careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
- Do not use more than one single dose of fosfomycin to treat a single episode of acute cystitis. Repeated daily dose increased the risk for adverse events.
- Reduced renal excretion in renal impairment (CrCl < 54 mL/min)
- Fosfomycin crosses the placental barrier. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, fosfomycin should be used during pregnancy only if clearly needed.

Interactions:[1-2]

- *Metoclopraminde*: when coadministered with fosfomycin increases gastrointestinal motility, lowers the serum concentration and urinary excretion of fosfomycin. Other drugs that increase gastrointestinal motility (e.g. erythromycin) may produce similar effects.
- *Sodium Picosulfate*: antibiotics may diminish the therapeutic effect of sodium picosulfate. Consider using an alternative product for bowel cleansing prior to a colonoscopy in patients who have recently used or are concurrently using an antibiotic.
- *Lactobacillus and Estriol:* antibiotics may diminish the therapeutic effect of lactobacillus and estriol.
- *BCG, Cholera and Typhoid vaccines (live attenuated Ty21a strain):* Systemic antibiotics may diminish the therapeutic effect of vaccine.

Adverse Reactions:[1-2]

In clinical trials, the most frequently reported adverse events occurring in >1% of the study population regardless of drug relationship were: diarrhea 10.4%, headache 10.3%, vaginitis 7.6%, nausea 5.2%, rhinitis 4.5%, back pain 3.0%, dysmenorrhea 2.6%, pharyngitis 2.5%, dizziness 2.3%, abdominal pain 2.2%, pain 2.2%, dyspepsia 1.8%, asthenia 1.7%, and rash 1.4%.

Cost Comparison:

Name	Treatment Duration (days)	Unit Cost	Total Cost
Fosfomycin 3 gm once	1	$79.38	$79.38
Nitrofurantoin 100 mg twice daily	5	$0.95	$9.50
Sulfamethoxazole /trimethoprim 800/160 mg twice daily	3	$0.12	$0.72

Guidelines:

The CDC Antibiotic Prescribing and Use in Doctor's Offices Adult Treatment Recommendations report that nitrofurantoin, trimethoprim/sulfamethoxazole (where local resistance is < 20%) and fosfomycin are all appropriate first-line

agents for the treatment of uncomplicated cystitis in health adult non-pregnant postmenopausal women. The CDC recommends that fluoroquinolones such as ciprofloxacin should be reserved for situations in which other agents are not appropriate.[3]

The International Clinical Practice Guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women also recommends nitrofurantoin 100 mg BID x 5 days, trimethoprim/sulfamethoxazole 160/800 mg (where local resistance is < 20%) BID x 3 days and fosfomycin 3 mg single dose as first-line empiric treatment options to consider (figure 1). If one of these agents cannot be used due to availability, allergy history, tolerance or resistance then use of a fluoroquinolone or β-lactam (not ampicillin or amoxicillin) may be considered.[4]

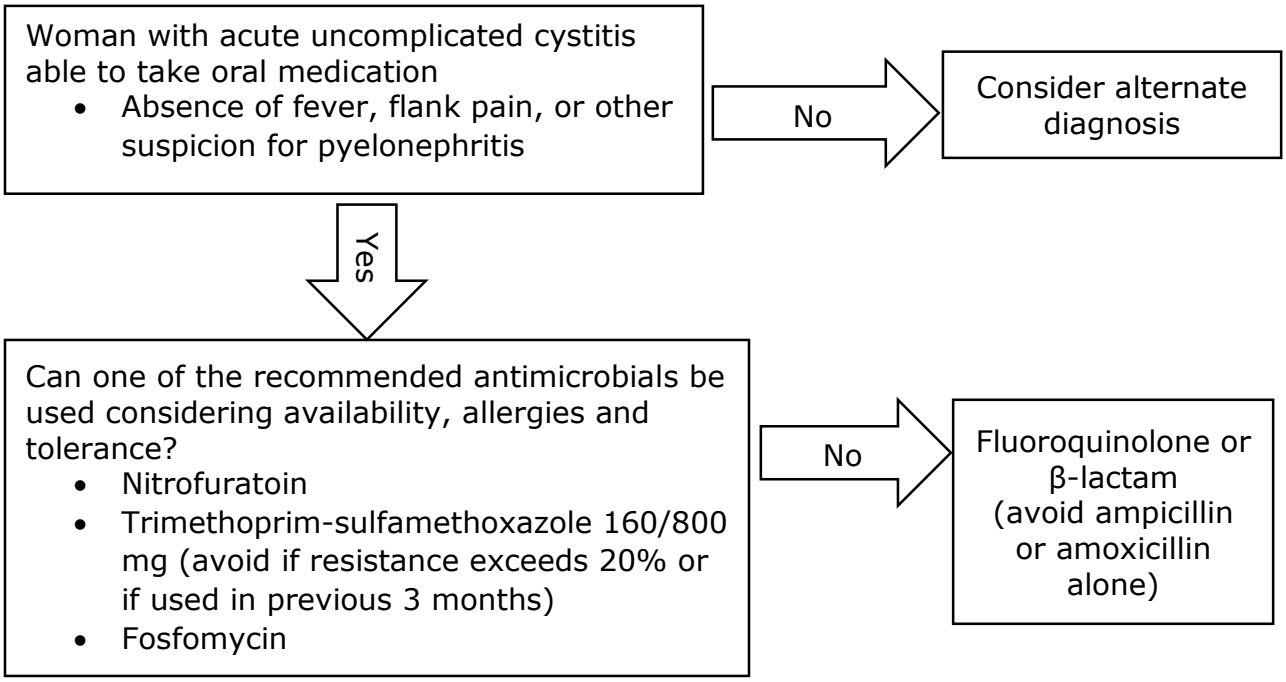

Figure 1: Algorithm for choosing empirical treatment of acute uncomplicated cystitis. Adapted from IDSA guidelines 2010.

Efficacy:

Efficacy of fosfomycin tromethamine has been well documented when compared to nitrofurantoin, trimethoprim/sulfamethoxazole, and fluoroquinolones. Fosfomycin tromethamine has a broad spectrum of activity against gram-negative and gram-positive uropathogens, is bactericidal and shows no cross-resistance with other antibiotics because of its unique chemical structure. It results in high concentrations in the urine with a low excretion rate allowing for single-dose treatment in uncomplicated cystitis in women.

<u>Fosfomycin vs. Nitrofurantoin</u>

One study evaluated the efficacy and tolerability of fosfomycin trometamol (n=116) in a single dose of 3 gm compared to nitrofurantoin (n=115) in a dose of 50 mg four times daily for 7 days. In this study, the 9 day cure rate was 81% for fosfomycin and 90% for nitrofurantoin. However, the overall 42 day post-treatment cure rate was 85% for fosfomycin and 82% for nitrofurantoin. The relapse/reinfection rate was 11% for fosfomycin and 13% for nitrofurantoin.

Statistically these differences were not significantly different. Fosfomycin treated patients reported more gastrointestinal side effects day 4 (fosfomycin 72% vs. nitrofurantoin 65%) and day 9 (fosfomycin 61% vs. nitrofurantoin 42%) of the study and symptoms were generally reported to be mild.[5]

Single-dose fosfomycin tromethamine (n=375) and multi-dose nitrofurantoin (n=374) were comparably efficacious in the treatment of uncomplicated UTI, in a randomized, multi-center, double-blind clinical trial. Women with uncomplicated UTI received either a 7 day regimen of twice daily nitrofurantoin 100 mg or a single-dose of fosfomycin 3 gm. Bacteriologic cure rates were similar for nitrofurantoin and fosfomycin at one week post-treatment (81% and 78%, respectively). Clinical cure rate was 80% for both drugs. There was no significant difference between groups with regard to re-infection rate, whereas fosfomycin treated patients experienced significantly fewer relapses compared with the nitrofurantoin treatment group. Adverse events were similar among the 2 groups, and were mild in severity.[6]

Pregnant patients attending antenatal clinics found to have significant bacteriuria without presenting UTI symptoms were evaluated. Patients were randomly allocated to receive either a single dose of fosfomycin trometamol one 3 gm sachet or nitrofurantoin 100 mg twice daily for 7 days. Bacteriological efficacy in 23 subjects were evaluated 15 days after therapy and then monthly until birth. Treatment response (cure) was reported to be similar for both groups, 84% with fosfomycin and 90% with nitrofurantoin. No adverse effects were reported with fosfomycin and 2 patients treated with nitrofurantoin reported adverse effects, one had nausea and the other nausea and vomiting.[7]

<u>Fosfomycin vs. trimethoprim/sulfamethoxazole</u>
Fosfomycin tromethamine (3 grams orally as a single dose) was found to be at least as effective as trimethoprim/sulfamethoxazole 960 milligrams orally daily for 3 days in uncomplicated urinary tract infections in one small study. In larger study, single oral doses of fosfomycin tromethamine (3 grams) and trimethoprim/sulfamethoxazole (1.92 grams) were similarly effective in treating female uncomplicated urinary tract infections. In both studies, the overall incidence and severity of adverse effects were similar with each agent, although diarrhea was observed more often with fosfomycin.[8]

Another study evaluated single dose fosfomycin trometamol 3 gm (n=224), co-trimoxazole (trimethoprim/sulfamethoxazole) 1.92 gm (n=109) and ofloxacin 200 mg (n=113) in female patients with acute uncomplicated UTI. Follow-up examinations occurred after one and four weeks in order to check for clinical and bacteriological success of therapy. At one week urine samples were sterile in 68.7%, 71% and 85.4% of fosfomycin, co-trimoxazole and ofloxacin treated patients with prior significant bacteriuria. At four weeks urine samples with nonsignificant pathogen counts were 81.9%, 79.4% and 80.8% of fosfomycin, co-trimoxazole and ofloxacin treated patients with prior significant bacteriuria. At four weeks persistent bacteriuria was present in 4.7%, 6.3% and 9% of fosfomycin, co-trimoxazole and ofloxacin treated patients. Gastrointestinal symptoms were the most commonly reported side effects and were similar among the treatment groups.[9]

In a randomized, comparative study in women with uncomplicated urinary tract infections, a single 3 gram dose of fosfomycin tromethamine was as effective as a

5-day course of ciprofloxacin. Women aged 18 to 65 years with uncomplicated urinary tract infections were randomized to receive either a single 3 gram oral dose of fosfomycin or ciprofloxacin 500 mg orally twice daily for 5 days. Primary efficacy outcomes were clinical response and bacteriological cure at follow-up. Escherichia coli and Enterobacter species were the most commonly isolated bacterial pathogens. For E coli, sensitivity was 94% and 59% for fosfomycin and ciprofloxacin. For Enterobacter, sensitivity was 75% and 85%, respectively. Bacteriological cure occurred in 83.1% in fosfomycin group and 78.4% for ciprofloxacin.[10]

Conclusions:
Fosfomycin has been shown to be effective in multiple studies with tolerability generally comparable to other antibiotics used in the treatment of UTI. Several trials have shown the efficacy of fosfomycin is similar to nitrofurantoin, trimethoprim/sulfamethoxazole and fluoroquinolone antibiotics such as ofloxacin and ciprofloxacin. Fosfomycin can be an appealing therapeutic option to treat uncomplicated UTI because it is a single-dose regimen and has few clinically relevant drug interactions. This antibiotic has relatively low use and an unshared mechanism of action with other antibiotics coupled with a low resistance rate. Fosfomycin is used to treat uncomplicated UTIs because of its broad spectrum of activity including resistant other pathogens associated with UTIs. However, compared to other first-line empiric antibiotic treatments, fosfomycin is more expensive than the other options.

Recommendation:
Consider the addition of fosfomycin to the formulary as it may be a beneficial empiric treatment option for uncomplicated UTI, particularly for those facilities with high trimethoprim/sulfamethoxazole resistance (>20%).

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