

**DADS/DSHS EXECUTIVE FORMULARY COMMITTEE MINUTES
July 24, 2015**

The Executive Formulary Committee convened on Friday, July 24, 2015 in Room 125 - ASH Building 552. The meeting was called to order by Dr. Wright, Chair at 9:35 a.m.

Phillip Balfanz, M.D.	√	Valerie Kipfer, MSN, RN (non-voting)	√
Mary Bowers RN, BSN	√	Lilani Muthali, M.D. (non-voting)	Absent
Catherine Hall, Pharm.D.	√	Nina Muse, M.D. (Acting Medical Director)	√
Jeanna Heidel, Pharm.D.	√	Jay Norwood, MSN, RN (non-voting)	Absent
Marla Knight, Pharm.D., CGP, FASCP	Absent	Peggy Perry (non-voting)	Absent
Jeff Matthews, M.D. (via phone)	√	Scott Schalchlin (non-voting)	Absent
Connie Millhollon, RN	√	Lauren Lacefield Lewis (non-voting)	Absent
Kenda Pittman, Pharm.D.	√	Kerry Raymond (non-voting)	Absent
Robert L. Ward, D.O.	√	Vacant Center Position	
Ann L. Richards, Pharm.D.	√	Vacant Center Position	
Archie Smith, M.D.	Absent	Vacant DADS Physician	
Jennifer Wright, M.D.	√		

Guests Present: Lisa Mican, Pharm.D., Austin State Hospital; Mikaela Farrell, Pharmacy Student ASH; Michelle Ding, Pharm.D., Resident ASH; Melissa Martinez, Pharmacy Student SASH; Isaac Pan, Pharm.D., Resident SASH

Introduction and Other Information

With Dr. Race's departure from Austin State Hospital, Dr. Ward, North Texas State Hospital was appointed as the newest member of the Committee.

Approval of Minutes of April 17, 2015

On a motion of Dr. Heidel, seconded by Dr. Balfanz, the minutes of the April 17th meeting were approved as previously distributed.

Conflict of Interest

Dr. Ward completed his disclosure statement and did not report any conflict of interest. None of the Committee members present reported any conflicts of interest.

Issues from the Medical Executive Committee

The Medical Executive Committee did not submit any issues to the Committee.

Adverse Drug Reaction Reports

The Executive Formulary Committee discussed three adverse drug reaction reports that were received from the field.

On April 24, 2015, montelukast (Singulair®) 10 mg at bedtime was prescribed for allergic rhinitis. The initial dose was given at 18:00 and at 19:20 a red rash to both lower legs and feet was noted. She has no known drug allergies. Her only allergy is to tomatoes. The rash was not raised, but described as very fine, sand-papery-like, maculopapular which appeared to be petechial. Vital signs were within normal limits at this time and the montelukast was put on hold. Within 24 to 36 hours, the rash was bright red, maculopapular and pruritic. Temperature was 99 degrees on April 26th and 100.3 degrees on April 27th. Diphenhydramine (Benadryl®) 25 mg every 6 hours x 48 hours was ordered along with CBC, CMP, UA, flu swab, strep screen, and chest x-ray. Chest x-ray showed no definite infiltrate, with some findings on left lung which may be bronchitis. Flu swab and strep screen were negative. The UA showed proteinuria (Nephrology consult pending). The CBC showed WBC up to 14.9 k/mm³ with repeat lab on April 28th and an ANC 11 k/mm³. Diagnoses were: 1. Prodromal illness, 2. viral rash, 3. URI. Augmentin® 875 – 125 mg BID per g-tube x10 days was started on April 28th. The rash was worse and spreading to upper arms at this time. A referral to a dermatologist was made and she was seen on April 30th. The dermatologist's diagnosis: Leukocytoclastic Vasculitis possibly due to montelukast. As of May 5th, the rash is still present but has begun to resolve. She received one dose only of the montelukast.

A 28 year old African American female was admitted to the state hospital in mid-January. Her diagnosis is schizophrenia since age 14 and 3 previous psychiatric hospitalizations with drug trials of risperidone (Risperdal®) and olanzapine (Zyprexa®) (unknown dose/duration) without reported adverse event or allergy. She denied medical history, family psychiatric history, or substance use. Labs were mostly within normal limits – CBC within normal limits (except low MCH 26.4 pg/cell), CMP within normal limits (except low albumin 2.9 g/dL, low total protein 6 g/dL), TSH within normal limit, and fasting lipid panel within normal limit. Serum pregnancy was negative and RPR was nonreactive. After court ordered medications were obtained; she was started on aripiprazole (Abilify®) 10 mg by mouth daily in early February for psychosis and was titrated to 30 mg by mouth daily over 6 weeks. She remained on the 30 mg dose for 2 weeks, but was still experiencing symptoms of psychosis and paranoia so it was tapered and discontinued. Risperidone (Risperdal®) 2 mg by mouth BID was initiated in mid-March and titrated to 3 mg by mouth BID after a few days with improvement in psychosis and paranoia. Approximately 1 month after initiation of risperidone, the patient complained of galactorrhea which she stated had been worsening over 2-3 days. On the day of her complaint, a prolactin level was drawn and found to be significantly elevated at 326.8 ng/mL at 7:10 am (normal range 2.8-29.2 ng/mL); the patient denied headache, excessive fatigue, blurry vision, irregular/abnormal menstruation (most recent menstrual cycle 2 weeks prior), and had not noticed any other abnormalities/changes. Risperidone was decreased to 2 mg twice daily. An MRI of the pituitary with and without contrast was performed and was within normal limits with no evidence of adenoma. Prolactin level was repeated after 1 week on the lower risperidone dose and it was still significantly elevated at 287.8 ng/mL at 8:15 am. Risperidone was then tapered and galactorrhea was noted to be improved 2 days before its discontinuation. Aripiprazole was restarted due to refusal of other antipsychotics. Galactorrhea completely resolved a few days after risperidone discontinuation. A repeat prolactin level 8 days after risperidone was discontinued was normal at 15.6 ng/mL.

A 46 year old male was taking quetiapine (Seroquel®) routinely since 8/21/2008. He has had regular (at least annual) eye exams during that time period. On 9/11/2013, the Optometrist reports a normal eye exam (“no ocular toxicity from quetiapine”) except for Pterygia, both eyes, stable. On 9/29/2014, the optometrist reports “the lens nucleus shows clouding and sclerosis. Mild opacification exists.” The impression is nuclear sclerotic cataracts. At this point, the patient was referred to an Ophthalmologist and was seen on 3/17/2015. The diagnosis was “Nuclear Sclerosis OU” and the examination revealed moderate senile nuclear cataracts, not visually significant. Since he has significant intellectual disability and was unable to

participate fully with the exam, the visual significance of the cataracts is in question. The PCP consulted psychiatry about stopping the quetiapine. It will be tapered and discontinued over the coming weeks. The PCP also consulted another Ophthalmologist regarding surgery for the cataracts since the treatment team cannot ascertain the visual significance of them and he is deaf and depends on his vision.

New Drug Applications

(Please refer to Attachment A for the monographs and applications that were considered when determining action by the committee.)

Moxifloxacin hydrochloride ophthalmic (Moxeza®, Vigamox®) - presented by Mikaela Farrell, Pharmacy student

Moxifloxacin ophthalmic is being considered for addition to the Formulary due to its nonformulary use. Moxifloxacin is a fourth generation fluoroquinolone that has broad spectrum activity against Gram-positive, Gram-negative, anaerobes and atypical microorganisms. It works by inhibiting the bacteria's topoisomerase II (DNA gyrase) and topoisomerase IV. Moxifloxacin is bactericidal. Moxifloxacin is used for the treatment of bacterial conjunctivitis caused by the following susceptible organisms:

- Gram positive microorganisms: *Corynebacterium species*, *Enterococcus faecalis*, *Micrococcus luteus*, *Staphylococcus arlettae*, *S. aureus*, *S. capitis*, *S. epidermidis*, *S. haemolyticus*, *S. hominis*, *S. saprophyticus*, *S. warneri*, *streptococcus mitis*, *S. pneumonia*, *S. parasanguinis*
- Gram negative microorganisms: *Acinetobacter lwoffii*, *Escherichia coli*, *Haemophilus influenza*, *Klebsiella pneumonia*, *Propionibacterium acnes*
- *Chlamydia trachomatis*

With regard to MRSA isolates, moxifloxacin may be the preferred fluoroquinolone.

Moxifloxacin ophthalmic is not available generically but is available in two different products with different dosages:

- Moxeza® - one drop in the affected eye two times daily for seven days
- Vigamox® - one drop in the affected eye three times daily for seven days

Moxifloxacin should be used for the treatment of bacterial conjunctivitis where MRSA is identified or suspected. Ciprofloxacin can still be used for contact wearers as long as MRSA is not suspected. In order to decrease the resistance, it was suggested that fluoroquinolones only be prescribed when necessary when MRSA or gram negatives are suspected.

Following discussion, on motion of Dr. Ward, seconded by Dr. Pittman, the request to add moxifloxacin ophthalmic (Moxeza®, Vigamox®) to the formulary was approved.

Rosuvastatin (Crestor®) - presented by Dr. Mican

Rosuvastatin selectively and competitively inhibits HMG-CoA reductase, the rate-limiting enzyme in the production of mevalonate, a cholesterol precursor. Rosuvastatin has high activity in, uptake into, and selectivity for the liver, the target organ. It enhances uptake and catabolism of LDL by increasing hepatic LDL receptor levels. It also inhibits the hepatic VLDL synthesis, reducing total number of VLDL and LDL particles. Rosuvastatin is indicated as adjunctive therapy to diet used for treatment of adult patients with primary hyperlipidemia or mixed dyslipidemia, treatment of heterozygous familial hypercholesterolemia (HeFH) in ages 10-17, hypertriglyceridemia, primary dysbetalipoproteinemia (Type III hyperlipoproteinemia), and slowing atherosclerosis progression. Adjunctive therapy to other lipid-lowering treatments to treat adults with homozygous familial hypercholesterolemia. It is also used to prevent cardiovascular disease by reducing risks of stroke, myocardial infarction, and arterial

revascularization procedures. Rosuvastatin dose range is 5 to 40 mg administered once daily. The usual starting dose is 10 to 20 mg. The dose can be administered any time of the day with or without food. The dose should be titrated based on the patient's response and goal of therapy. Lipid levels should be analyzed 2 to 4 weeks after initiation or titration of therapy and adjusted accordingly. The 40 mg dose should only be used in patients who did not achieve LDL-C goal with the 20 mg dose. Asian patients have increased plasma rosuvastatin levels; therefore a starting dose of 5 mg once daily should be considered.

Following discussion, on motion of Dr. Hall, seconded by Dr. Wright, the request to add rosuvastatin (Crestor®) to the formulary as a reserve drug was approved. On a motion of Dr. Ward, seconded by Dr. Heidel, the reserve criteria for using rosuvastatin were recommended to be: “for those patients needing high intensity statin therapy with nonresponse or significant drug-drug interactions with atorvastatin (Lipitor®).” Since the patent for rosuvastatin will expire in 2016; it was recommended that the rosuvastatin be reviewed in one year or when a generic is available.

Drug Deletions

The following drug products were recommended for deletion based on April's sectional review:

Generic Name	Brand Name	Dosage forms to be deleted	Dosage forms still available
Amoxapine	Asendin®	Tablet: 25 mg, 50 mg, 100 mg, 150 mg	None
Maprotiline	Ludiomil®	Tablet: 25 mg, 50 mg, 75 mg	None
Trimipramine	Surmontil®	Capsule 25 mg, 50 mg, 100 mg	None

No responses were received from the field. On a motion of Dr. Heidel, seconded by Dr. Matthews, the recommendation to delete these products was approved.

New Dosage Strengths

The Committee did not consider any dosage strength addition to the Formulary.

Quetiapine (Seroquel®, Seroquel® XR) Purchases

The following is a summary of Seroquel® and Seroquel® XR purchases for the State Hospitals since the Committee started monitoring the purchases:

EFC Meeting Date	Reporting Period	Purchases
July 2012	April - June 2012	\$5,117.34
October 2012	July - September 2012	\$11,575.85
January 2013	October - December 2012	\$6,246.34
April 2013	January - March 2013	\$15,017.84
July 2013	April - June 2013	\$17,266.15
October 2013	July - September 2013	\$24,820.16
January 2014	October - December 2013	\$7,262.08
April 2014	January - March 2014	\$6,192.07
July 2014	April - June 2014	\$0.00
October 2014	July - September 2014	\$0.00
January 2015	October - December 2014	\$1,221.25
April 2015	January - March 2015	\$0.00
July 2015	April - June 2015	\$0.00

Quetiapine became generic in the spring of 2012. Since the purchases of the Seroquel® products have decreased significantly and have been zero for four of the last five monitoring periods, it was recommended that this item be dropped from reporting. The purchases will still be monitored just not reported to the Committee unless an issue arises.

Dexmethylphenidate (Focalin®) Purchases

At the last meeting, it was recommended that the purchase history of dexmethylphenidate be obtained due to its non-formulary use. From July 1, 2014 to June 30, 2015 the following purchases were made:

Facility Type	Brand	Generic	Total
State Hospitals	\$8,835.56	\$1,869.29	\$10,704.85
State Supported Living Centers	\$7,614.89	\$1,419.30	\$9,034.19

On a motion of Ms. Millhollon, seconded by Dr. Ward, it was recommended that dexmethylphenidate purchases for the quarter (July through September) be reviewed at the next meeting in order to determine the potential for Formulary consideration.

Metabolic Syndrome – BMI vs. Waist Circumference

The question arose as to whether or not one should use BMI or waist circumference for detecting and monitoring metabolic syndrome. The ATP III guidelines identify metabolic syndrome as the presence of any three of the following five traits:

- Abdominal obesity, defined as a waist circumference in men ≥ 102 cm (40 inches), women ≥ 88 cm (35 inches)
- Serum triglycerides ≥ 150 mg/dL or drug treatment for elevated triglycerides
- Serum high-density lipoprotein (HDL) cholesterol < 40 mg/dL in men and < 50 mg/dL in women or drug treatment for low HDL cholesterol
- Blood pressure $\geq 130/85$ mmHg or drug treatment for elevated blood pressure
- Fasting plasma glucose (FPG) ≥ 100 mg/dL or drug treatment for elevated blood glucose

Janssen and colleagues reported that the patient's waist size is also a useful risk indicator for high blood pressure, type II diabetes, dyslipidemia, and metabolic syndrome. For women, having a waist size of 35 inches or more was associated with these risk factors regardless of their BMI category (normal, overweight, or obese). For men, having a high-risk waist measurement incurred somewhat less health risk if their BMI was in the normal range. (Janssen I, Katzmarzyk PT, Ross R: Body mass index, waist circumference, and health risk. Arch Intern Med 2002. 172:2074-2079)

The Mount Sinai Conference recommended the following:

- Clinics that provide treatment for patients with schizophrenia should have the capability of weighing patients at every visit and of tracking those weights. BMI monitoring should be supplemented by measurement and recording of the patient's waist circumference. Patients should be weighed/measured at every visit for the first six months after medication initiation or change.
- Unless a patient is underweight (BMI < 18.5), a weight gain of one BMI unit indicates a need for an intervention. Mental health providers should also initiate an intervention if the patient's waist circumference is 35 inches or greater for a woman and 40 inches or greater for a man.

Marder SR, Essock SM, Miller AL, Buchanan RW, Casey DE, Davis JM, et al, et al. Physical Health Monitoring of Patients With Schizophrenia. Am J Psychiatry. 2004;161:1334-1349.

The ADA/APA Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes (Diabetes

Care, Volume 27, Number 2, February 2004) stated:

- Clinicians who prescribe SGAs for patients with psychiatric illnesses should have the capability of determining a patient's height and weight (BMI) and waist circumference.
- Recommendation:
 - Waist circumference (at the level of the umbilicus) at baseline and annually

The Belgian consensus on metabolic problems associated with atypical antipsychotics (International Journal of Psychiatry in Clinical Practice. 2005;9(2):130-137) stated:

- Patients should be counselled about measuring and charting their own weight and waist circumference.
- Recommendation:
 - Weight and waist circumference (to be measured in the middle between iliac crest and lower rib cartilage) at baseline, weekly in hospital care, monthly in ambulatory care.

The Psychotropic Audit Criteria and Guidelines currently require BMI monitoring for typical antipsychotics, including thioridazine, fluphenazine decanoate and haloperidol decanoate and atypical antipsychotics including clozapine. This requirement is the same for all antipsychotics and is:

BMI measurement – when a new antipsychotic is initiated, at every visit (monthly for inpatients) for 6 months after the new antipsychotic is initiated and quarterly when the antipsychotic dose is stable.

It was reported that many of the facilities are already obtaining waist circumferences. However, it was noted that some of these measurements vary significantly from month to month. The Committee discussed the need to have an accurate measurement if waist circumference becomes a monitoring parameter. The Committee suggested that initial and annual training on taking a waist circumference plus a return demonstration of competency would assist in minimizing these variations.

After reviewing the information, on a motion of Ms. Millhollon, seconded by Dr. Pittman, it was recommended that the waist circumference be added to the BMI monitoring requirement for antipsychotics at the exact same frequency as the BMI. In addition, it was recommended that that staff be trained initially and annually on the correct method for obtaining a waist circumference and that a return demonstration of competency be completed in order to successfully pass the training.

Dr. Richards will update the antipsychotic audit guidelines and criteria to reflect this change in monitoring.

Psychotropic Audit Criteria and Guidelines – Purpose of Laboratory Monitoring

In reviewing “Appendix A” for the Psychotropic Audit Criteria and Guidelines, it was noted that previously obtained laboratory results could be used for the baseline lab requirements as long as the results were documented in the record and were obtained within 90 days of initiation of treatment and if there are no intervening illnesses within those 90 days which would necessitate repeating the lab work. A time parameter for obtaining an EKG is not addressed in “Appendix A.” Since it is reasonable to accept a baseline EKG from another facility, it was recommended that similar statements regarding the acceptance of a baseline EKG be added to “Appendix A.”

On a motion of Dr. Heidel, seconded by Ms. Millhollon, the recommendation to add baseline parameters regarding EKGs to the “Medication Audit Criteria and Guidelines: Purpose of Laboratory Monitoring (Appendix A)” was approved. See Attachment B.

Antipsychotic Plasma Levels

At the last meeting, it was recommended that guidelines for obtaining antipsychotic plasma levels be developed. Dr. Hall provided a review “AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Psychiatry: Update 2011” (Pharmacopsychiatry 2011;44:195-235). The following are considered to be Level 1 (strongly recommended)

for using therapeutic drug monitoring:

Drug	Therapeutic reference range/ Recommended drug concentration
Amisulpride*	100 – 320 ng/ml
Clozapine	350 – 600 ng/ml
Fluphenazine	1 – 10 ng/ml
Haloperidol	1 – 10 ng/ml
Olanzapine	20 – 80 ng/ml
Perazine*	100 – 230 ng/ml
Perphenazine	0.6 – 2.4 ng/ml
Thioridazine	100 – 200 ng/ml

* Not available in the United States

In addition, the AGNP Consensus Guidelines provided a list of typical indications for measuring plasma concentrations of medications in psychiatry. The following indications were listed:

- Dose optimization after initial prescription or after dose change
- Drugs, for which TDM is mandatory for safety reasons (e.g., lithium)
- Suspected complete or partial non-adherence (non-compliance) to medication
- Lack of clinical improvement under recommended doses
- Adverse effects and clinical improvement under recommended doses
- Combination treatment with a drug known for its interaction potential or suspected drug interaction
- TDM in pharmacovigilance programs
- Relapse prevention under maintenance treatment
- Recurrence under adequate doses
- Presence of a genetic particularity concerning drug metabolism (genetic deficiency, gene multiplication)
- Pregnant or breast feeding patient
- Children and adolescent patient
- Elderly patient (>65 years)
- Individuals with intellectual disabilities
- Patients with pharmacokinetically relevant comorbidities (hepatic or renal insufficiency, cardiovascular disease)
- Forensic patient
- Problems occurring after switching from an original preparation to a generic form (and vice versa)

On a motion of Dr. Hall, seconded by Dr. Ward, it was recommended that the indications for measuring plasma concentrations of medications in psychiatry as provided by the “AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Psychiatry: Update 2011” (Pharmacopsychiatry 2011;44:195-235) be approved.

Psychotropic Audit Criteria & Guidelines - Antidepressants

The Antidepressant Audit Criteria and Guidelines have not been reviewed.

Psychotropic Audit Criteria & Guidelines – Chemical Dependence Adjunct

The Chemical Dependence Adjunct Audit Criteria and Guidelines have not been developed.

Hydroxyzine – QTc Interval Follow Up and Audit

At the last meeting, the hydroxyzine recommendations made by the European Medicine Agency Pharmacovigilance

Risk Assessment Committee (PRAC) were reviewed. Since then, the European group Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) approved the recommendations by PRAC. At this time, the FDA has not acted.

At the last meeting, it was recommended that a system-wide audit for hydroxyzine be developed and implemented. At this time, the audit should be released to the field in the next two weeks.

Formulary Status of Required Vaccines

Between the State Hospitals and the State Supported Living Centers, the following vaccines are required for employees:

- Measles, Mumps, Rubella (MMR)
- Varicella
- Hepatitis B
- Influenza
- Pertussis

Pertussis is a component of diphtheria, tetanus and acellular pertussis (Tdap) vaccine. All of the required vaccines are on our Formulary.

Drug Formulary Sectional Review-

Gastrointestinal Agents Muscle Relaxant Agents

Dr. Hall provided the review on the agents in the Psychotropic section. Ms. Debra Gregg, Assistant Director at San Antonio State Hospital assisted in the review of the drug products. Based on their review, the following recommendations were made:

- Delete the following from the Formulary due to lack of availability:

Generic Name	Brand Name	Dosage forms to be deleted	Dosage forms still available
Aluminum hydroxide	Amphojel®	Capsule: 400 mg Tablet: 300 mg, 400 mg, 500 mg, 600 mg	Suspension, oral: 320 mg/5 ml; 600 mg/5 ml
Aluminum hydroxide – magnesium hydroxide		Tablet	Suspension, oral
Dicyclomine	Bentyl®	Capsule: 20 mg Tablet: 10 mg	Capsule: 10 mg Injection: 10 mg/ml Syrup: 10 mg/5 ml
Propantheline	Pro-Banthine	Tablet: 7.5 mg	Tablet: 15 mg
Ranitidine	Zantac®	Granules, effervescent: 150 mg Tablet, effervescent: 150 mg	Injection: 25 mg/ml Syrup: 15 mg/ml Tablet: 75 mg, 150 mg, 300 mg
Lansoprazole	Prevacid®	Granules for oral suspension: 15 mg, 30 mg	Capsule, enteric coated granules: 15 mg, 30 mg
Simethicone	Mylicon®	Tablet, chewable: 40 mg	Drops, oral: 40 mg/0.6 ml Tablet, chewable: 80 mg, 125 mg
Magnesium hydroxide	Milk of Magnesia	Liquid, oral, concentrate: 800 mg/5 ml	Liquid, oral: 400 mg/5 ml Tablet, chewable: 311 mg
Senna	Senokot®	Tablet: 25 mg	Tablet: 8.6 mg
Polycarbophil	Fibercon®, Fiber-	Tablet: 600 mg, 650 mg	Tablet: 500 mg, 625 mg

Generic Name	Brand Name	Dosage forms to be deleted	Dosage forms still available
	Lax®		
Docusate sodium	Colace®	Tablet: 100 mg	Capsule: 100 mg, 250 mg Liquid, oral: 150 mg/15 ml Syrup: 60 mg/15 ml
Pramoxine	Tronothane®	Ointment, topical: 1%	Cream, topical: 1% Gel, topical: 1% Lotion: 1% Spray: 1%
Rectal Hemorrhoidal Suppositories – Hydrocortisone	Anusol-HC®	Suppositories, rectal, as acetate: 10 mg	Suppositories, rectal, as acetate: 25 mg
Activated Charcoal		Capsule: 200 mg Liquid, oral, activated, with sorbitol: 30 g Tablet: 260 mg	Capsule: 260 mg, Liquid, oral, activated, with sorbitol: 25 g, 50 g Oral suspension, activated: 15 g, 30 g, 40 g, 120 g, 240 g
Mesalamine	Asacol®, Pentasa®, Rowasa®	Suppository: 500 mg Tablet, delayed release: 400 mg	Capsule, extended release: 250 mg Suppository: 1,000 mg Suspension, rectal: 4 gm/60 ml

- Delete the strengths from the calcium carbonate listing. Consider all strengths of oral calcium carbonate liquid, tablets and chewable tablets as being on formulary
- Change the brand name of lactulose from Cephulac® to Enulose®
- Delete the brand name OCL from propylene glycol electrolyte solution
- Delete the brand name Doxinate® from docusate sodium
- Change the “Powder for oral suspension, activated” entry in the Activated Charcoal listing to “Oral suspension, activated”
- Change the “Capsule, controlled release” entry in the Mesalamine listing to “Capsule, extended release”
- Format the Muscle Relaxant section into:
 - Muscle Relaxant Agents
 - Cyclobenzaprine
 - Diazepam
 - Methocarbamol
 - Antispasticity Agents
 - Baclofen
 - Dantrolene
 - Diazepam
 - Tizanidine

- Add the following to the Formulary

Generic Name	Brand Name	Dosage forms to be added
Dicyclomine	Bentyl®	Tablet: 20 mg
Ranitidine	Zantac®	Tablet, effervescent: 25 mg
Magnesium hydroxide	Milk of Magnesia	Liquid, oral concentrate: 1,200 mg/5 ml
Docusate sodium	Colace®	Capsule: 50 mg
Pramoxine – hydrocortisone	Analpram HC	Cream: pramoxine 1% with hydrocortisone 2.5%
Mesalamine	Asacol®, Pentasa®, Rowasa®	Tablet, delayed release: 800 mg

On a motion of Dr. Ward, seconded by Dr. Heidel, the recommended changes to the Formulary were approved. Since the products were deleted due to lack of availability, feedback will not be obtained from the field.

FDA Drug Safety Communications

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

The FDA is warning that permanent loss of skin color may occur with use of the methylphenidate transdermal system (Daytrana® patch) for Attention Deficit Hyperactivity Disorder (ADHD). The FDA added a new warning to the drug label to describe this skin condition, which is known as chemical leukoderma. Chemical leukoderma is a skin condition that causes the skin to lose color due to repeated exposure to specific chemical compounds. The condition is not physically harmful, but it is disfiguring. The areas of skin color loss described with the methylphenidate transdermal patch ranged up to 8 inches in diameter. This condition is not thought to be reversible, which may cause emotional distress. Patients or their caregivers should watch for new areas of lighter skin, especially under the drug patch, and immediately report these changes to their health care professionals. The FDA recommends that health care professionals consider alternative treatments for patients who experience these skin color changes.

The FDA is strengthening an existing label warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) increase the chance of a heart attack or stroke. Based on FDA's comprehensive review of new safety information, the FDA is requiring updates to the drug labels of all prescription NSAIDs. As is the case with current prescription NSAID labels, the Drug Facts labels of over-the-counter (OTC) non-aspirin NSAIDs already contain information on heart attack and stroke risk. The FDA will also request updates to the OTC non-aspirin NSAID Drug Facts labels.

Prescription NSAID labels will be revised to reflect the following information:

- The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID.
- The risk appears greater at higher doses.
- It was previously thought that all NSAIDs may have a similar risk. Newer information makes it less clear that the risk for heart attack or stroke is similar for all NSAIDs; however, this newer information is not sufficient for us to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.
- NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. A large number of studies support this finding, with varying estimates of how much the risk is increased, depending on the drugs and the doses studied.
- In general, patients with heart disease or risk factors for it have a greater likelihood of heart attack or stroke following NSAID use than patients without these risk factors because they have a higher risk at baseline.
- Patients treated with NSAIDs following a first heart attack were more likely to die in the first year after the heart attack compared to patients who were not treated with NSAIDs after their first heart attack.
- There is an increased risk of heart failure with NSAID use.

Patients and health care professionals should remain alert for heart-related side effects the entire time that NSAIDs are being taken. Patients taking NSAIDs should seek medical attention immediately if they experience symptoms such as chest pain, shortness of breath or trouble breathing, weakness in one part or side of their body, or slurred speech.

Medical Director for Behavioral Health

Dr. Muse shared a draft copy of the DSHS Operating Procedures for "Treatment of Hepatitis C with Direct-Acting Antiviral Medication." The eligibility criteria for receiving direct-acting antiviral medication is based on the Medicaid eligibility. The proposed approval process is: approval by the facility Clinical Director, then the Medical

Director for Behavioral Health, then Assistant Commissioner for Behavioral Health. The Assistant Director for Behavioral Health will consult with staff about the availability of funds to support the treatment and approves/denies the request. No matter the source of funding, the approval process needs to be followed.

Quarterly Non-Formulary Drug Justification Report

For the third quarter of fiscal year 2015, all facilities reported use of non-formulary agents. The DADS facilities submitted 927 non-formulary requests and the DSHS facilities had 458 requests. The following were the top non-formulary agents that were prescribed:

- Omega-3 product
- Levalbuterol (Xopenex®)
- Fiber-Stat Natural solution packets
- Losartan (Cozaar®)
- UTI-Stat Liquid
- Saccharomyces boulardii capsule (Florastor®)

Sectional Review for Next Meeting

The following section will be reviewed at the next meeting:

- Infectious Disease Agents
- Antineoplastic Agents
- Formulary Table Review
- Reserve Drug List

Other Issues

The following information was shared with the Committee members:

From CredibleMeds®:

In 2005, CredibleMeds® created a new risk category for drugs, i.e., those with Conditional Risk of torsades de pointes (TdP). This category includes those drugs for which we found strong and convincing evidence of TdP but only under certain clinical conditions and not when used as directed. These conditions included extreme bradycardia, low serum K⁺ or Mg⁺⁺, drug overdose or when the drug's elimination is impaired by another drug (i.e. due to interactions with other prescribed drugs). We also included drugs that have evidence of causing TdP because they create conditions that foster TdP, i.e. drugs that block the elimination of a QT prolonging drug or that cause low serum K⁺ or Mg⁺⁺, e.g. certain diuretics. We have recently reviewed the data now available for the drugs in the Conditional Risk category. We found that the evidence for increased QT or TdP was not convincing for two drugs, amoxapine and protriptyline. Therefore, these drugs will be removed from all lists on the CredibleMeds website and monitored closely.

We found convincing evidence of QT prolongation for clomipramine, desipramine, imipramine, nortriptyline and trimipramine but no convincing evidence of TdP. Therefore, these drugs will be moved from the Conditional Risk list to the Possible Risk list of drugs that have the ability to prolong QT but lack substantial evidence that they cause TdP.

Note that the drugs moved from Conditional Risk to the Possible Risk list will still remain on the list of Drugs to Avoid for patients with congenital LQTS.

HealthDay reports that a review published May 19 in the Journal of the American Medical Association suggests that "antidepressants seem to help women deal with postpartum depression." Researchers arrived

at that conclusion after examining the results of “six studies that included nearly 600 women with postpartum depression,” then focusing “their analysis on 72 women with postpartum depression from three of the studies.”

MedPage Today reports that the selective estrogen receptor modulator raloxifene, a medication “aimed at preventing osteoporosis, appears to help the cognitive deficits associated with schizophrenia,” according to the results of a 93-patient study presented at the American Psychiatric Association’s annual meeting and published online May 18 in *Molecular Psychiatry*

Reuters reports that US District Judge George Hazel issued a final ruling against Otsuka Pharmaceutical Co. Ltd. in its challenge of the Food and Drug Administration’s decision permitting generic versions of Otsuka’s antipsychotic Abilify® (aripiprazole). Otsuka had claimed that the medication had orphan status because it had been approved to treat pediatric Tourette syndrome, but Judge Hazel rejected the argument, pointing out that the medication had non-pediatric uses not covered by orphan status.

The Wall Street Journal reported that drug shortages have become a continual problem, with the number of drugs in short supply rising 74% over the past five years to approximately 265, according to the University of Utah’s Drug Information Service. Experts point to several causes, including a lack of production capacity, improper equipment maintenance, and contamination in older plants. A considerable amount of the drugs in short supply are older injectable treatments that are often complicated and expensive to manufacture, but have comparatively low prices because they lack patent protection. In response to production complications, pharmaceutical manufacturers of these drugs are often unable to increase prices because of limitations on reimbursement for hospital-administered drugs.

NBC Nightly News reported on “a big wake-up call for the millions of Americans who take certain kinds of sleeping” medications. Correspondent Ann Thompson explained, “A new study...finds three sedatives nearly double the risk of vehicle accidents among new users.” In addition, “the study...finds the risk of accidents increases over time and can last up to a year after you start taking the drugs.” The NBC News website reports that for the study, investigators “collected data on...zolpidem, sold under the brand name Ambien; trazodone, sometimes sold under the brand name Olepro; and temazepam, brand name Restoril.” The researchers found “that people who took any one of” these “three popular sleeping aids had anywhere between a 25 percent and three times higher risk of being involved in an accident while driving.” The study was published online in the *American Journal of Public Health*.

Medscape reports that the FDA announced today that “the potential risks for vision loss due to pigment changes in the retina, and for skin discoloration” associated with GlaxoSmithKline’s antiseizure drug Potiga (ezogabine) “can be adequately managed by following the current recommendations on the drug’s labeling.” However, the FDA “has required GlaxoSmithKline to conduct a long-term observational study to further investigate any potential long-term consequences of these pigment changes.”

MedPage Today reported that a “retrospective analysis of Veterans Affairs data” presented during a poster session at the Movement Disorders Society meeting reveals that patients with Parkinson’s disease who take antipsychotics may be “twice as likely to die in the 180 days after starting therapy compared with those not on” those medications.

MedPage Today reported, “Treatment with the investigational agent pimavanserin significantly reduced hallucinations and delusions that frequently occur in patients with Parkinson’s disease,” according to the results of a 133-patient study presented at the International Congress of Parkinson’s Disease and Movement Disorders.

Medscape reports that the Food and Drug Administration “has expanded the indication for the antiepileptic drug (AED) perampanel hydrate (Fycompa, Eisai Inc) as adjunctive therapy for primary generalized tonic-clonic (PGTC) seizures in patients with epilepsy 12 years of age and older,” according to the company. The drug “is a first-in-class highly selective AMPA receptor antagonist first approved in the United States as adjunctive therapy for partial-onset seizures with or without secondarily generalized seizures in patients aged 12 years and older in 2012.” The new indication is based on clinical studies of 164 patients that “showed a statistically significant reduction in PGTC seizure frequency with perampanel compared with placebo (change, -76.5% vs -38.4%; $P < .0001$).”

USA Today reported that a combination of ketamine and the tuberculosis medication D-cycloserine may help treat treatment-resistant bipolar depression, according to an eight-patient study. Researchers found that adding the tuberculosis medicine to ketamine helped prolong the latter’s effects and resulted in an average “50% reduction in symptoms of depression and a 75% reduction in the likelihood of patients committing suicide.”

MedPage Today reports, “Women taking selective serotonin reuptake inhibitors (SSRIs) to treat menopausal symptoms are up to 76% more likely to break a bone,” according to a study published in Injury Prevention. After studying “more than 137,000 women ages 40 to 64 with no mental health issues who started SSRIs between 1998 and 2010,” researchers also found that “the increased risk persists for at least five years following initiation of SSRI treatment, suggesting that shortening treatment could reduce the risk.” The National Institute of Mental Health and the National Institute on Aging supported the study.

HealthDay reports that research published in PLOS ONE suggests that statins may “influence a person’s aggressive behaviors, increasing or decreasing their irritability and violent tendencies.” Researchers found that “men taking statins typically become less aggressive, while women on statins tend to become more aggressive.”

The Washington Post “To Your Health” blog reports in continuing coverage that a study published online July 1 in JAMA Psychiatry suggests that antipsychotic medication “use has been on the rise among adolescents, even though most had not been diagnosed with a mental disorder.” After analyzing “data from thousands of prescriptions to analyze trends between 2006 and 2010,” investigators also “expressed concern that in cases where there are diagnosed mental disorders, the antipsychotic drugs are being used to treat unapproved conditions, such as attention-deficit/hyperactivity disorder and depression.”

The Los Angeles Times reports in “Science Now” that the “Vital Signs” report in the CDC’s Morbidity and Mortality Weekly Report found that “2.6 out of every 1,000 US residents 12 and older used heroin in the years 2011 to 2013,” representing “a 63% increase in the rate of heroin use since the years 2002 to 2004.” Over that same period of time, “the rate of heroin abuse or dependence climbed 90%...according to the study by researchers from the US Food and Drug Administration and the Centers for Disease Control and Prevention.”

USA Today reports that the selective serotonin reuptake inhibitor (SSRI) “antidepressants Paxil [paroxetine hydrochloride] and Prozac [fluoxetine] are linked to higher rates of birth defects, but several similar drugs used to treat depression in pregnant women carry no such risks,” according to a study conducted by the CDC and published July 8 in the BMJ. For the study, researchers “analyzed conflicting results from previous studies along with new data on nearly 28,000 births.”

The Washington Post reports that US consumers spend approximately \$1.2 billion each year for fish oil supplements and related products “even though the vast majority of research published recently in major journals provides no evidence of a health benefit.”

Reuters reported that the Food and Drug Administration on Friday approved H. Lundbeck A/S and Otsuka Pharmaceutical Co Ltd.’s new schizophrenia treatment, Rexulti (brexpiprazole). The medicine was also approved to treat major depressive disorder as an adjunctive therapy.

In continuing coverage, the Washington Post “To Your Health” blog reported that a “population-based study, published in the BMJ, found that mixing antidepressants with common painkillers appears to be linked to a higher risk of intracranial bleeding...shortly after starting the treatment.” Researchers “found that during that initial 30-day window of antidepressant use, 742 people experienced intracranial bleeding, with 169 on antidepressants only and 573 taking both antidepressants and NSAIDs.” Interestingly, “there were no significant differences based on which antidepressants...were taken or the age of the person.” Men appeared to have a greater risk than women did for such bleeding.

The Wall Street Journal reports in “Pharmalot” that Gilead Sciences is limiting the enrollment of its patient assistance program that provides hepatitis C drugs to those who cannot otherwise afford them. The author claims the move is designed to put pressure on insurers that have restricted patient access to the drugs.

Next Meeting Date

The next meeting was scheduled for October 30, 2015.

Adjourn

There being no further business, the meeting was adjourned at 2:02 p.m.

Approved: *Jennifer Wright*
Jennifer Wright, M.D., Chairman

Attachments

- Attachment A – New Drug Applications
- Attachment B – Purpose of Laboratory Monitoring

Minutes Prepared by:

Ann L. Richards, Pharm.D., BCPP

APPENDIX 1: NEW DRUG APPLICATION FORM

415 — C
EXHIBIT A

TEXAS DEPARTMENT OF MENTAL HEALTH AND MENTAL RETARDATION

NEW DRUG APPLICATION
(for inclusion in the *TDMHMR Drug Formulary*)

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

Date: 7/16/15

Name of practitioner submitting the application: Dr Cathey

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	<u>Antihyperlipidemic</u>
Generic Name	<u>Rosuvastatin</u>
Trade Name(s)	<u>Crestor</u>
Manufacturer(s)	<u>AstraZeneca</u>
Dosage Form(s)	<u>5 mg, 10 mg, 20 mg, 40 mg tablets</u>

Explain the pharmacological action or use of this drug:

HMG-CoA reductase inhibitor

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

High intensity statin therapy with no significant CYP interactions potent LDL ↓
atorvastatin TG ↓ & can ↑ HDL

State which drugs this new drug would replace or supplement:

application is approved

OR

application is appropriate and complete

[Signature]
signature of chairman of facility pharmacy and therapeutics committee

[Signature]
signature of clinical/medical director or designee

Attachment A-1

Rosuvastatin Calcium (Crestor[®], AstraZeneca)

Classification: Antihyperlipidemic, Cardiovascular Agent, HMG-CoA Reductase Inhibitor¹

Pharmacology:

Rosuvastatin selectively and competitively inhibits HMG-CoA reductase, the rate-limiting enzyme in the production of mevalonate, a cholesterol precursor. Rosuvastatin has high activity in, uptake into, and selectivity for the liver, the target organ. It enhances uptake and catabolism of LDL by increasing hepatic LDL receptor levels. It also inhibits the hepatic VLDL synthesis, reducing total number of VLDL and LDL particles.¹

Pharmacokinetics:

Absorption: Peak plasma concentrations reached 3-5 hours after oral dose. C_{max} and AUC proportionately increases with rosuvastatin dose. Bioavailability 20%. Food has no effect on AUC. AUC does not differ between morning and evening doses.^{1,2}

Distribution: Volume of distribution 134 L, 88% protein bound (mostly albumin)¹

Metabolism: Not extensively metabolized; major metabolite has one-sixth to one-half inhibitory activity of parent. Greater than 90% of activity attributed to parent compound.¹

Elimination: Oral: 90% excreted in feces; elimination $t_{1/2}$ 19 hours. IV: 28% renally cleared; 72% hepatically cleared¹

Indications:

Adjunctive therapy to diet used for treatment of adult patients with primary hyperlipidemia or mixed dyslipidemia, treatment of heterozygous familial hypercholesterolemia (HeFH) in ages 10-17, hypertriglyceridemia, primary dysbetalipoproteinemia (Type III hyperlipoproteinemia), and slowing atherosclerosis progression. Adjunctive therapy to other lipid-lowering treatments to treat adults with homozygous familial hypercholesterolemia. Also used to prevent cardiovascular disease by reducing risks of stroke, myocardial infarction, and arterial revascularization procedures.¹

Dosage:

General: rosuvastatin dose range is 5 to 40 mg orally once daily. Starting dose is usually 10 to 20 mg. Can administer single dose any time of the day with or without food. Swallow tablets whole. When initiating rosuvastatin or switching from another HMG-CoA reductase inhibitor, use appropriate starting dose then titrate based on patient's response and goal of therapy. Lipid levels should be analyzed 2 to 4 weeks after initiation or titration of therapy and adjust dose accordingly. 40 mg dose should only be used in patients who did not achieve LDL-C goal with 20 mg dose.^{1,2}

HeFH in pediatrics patients: usual rosuvastatin dose is 5-20 mg/day; max 20 mg/day; dose adjustments at intervals of 4 weeks or more.¹

Homozygous familial hypercholesterolemia: recommended rosuvastatin starting dose is 20 mg once daily; asses response to therapy from preapheresis LDL-C levels.¹

Asian patients have increased plasma rosuvastatin levels; consider 5 mg once daily as initial dose.¹

Use with concomitant therapy:

Patients concomitantly taking cyclosporine: rosuvastatin max dose of 5 mg once daily.

Patients concomitantly taking gemfibrozil: rosuvastatin initial therapy of 5 mg once daily; should not exceed 10 mg once daily.

Patients concomitantly taking lopinavir and ritonavir or atazanavir and ritonavir: rosuvastatin initial therapy of 5 mg once daily; should not exceed 10 mg once daily.¹

Patients with severe renal impairment (CrCl < 30 mL/min/1.73m²) not on hemodialysis should initiate rosuvastatin therapy at 5 mg once daily; should not exceed 10 mg once daily. Plasma concentration is increased 3-fold in severe renal impairment.¹

Contraindications

- Known hypersensitivity to any component of product. Reported hypersensitivity reactions include rash, pruritis, urticaria, and angioedema
- Active liver disease including unexplained persistent hepatic transaminase level elevations
- Pregnant or may become pregnant
- Nursing mothers¹

Warnings and Precautions:

- Risk of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria; risk increased with highest dose (40 mg)
- Caution when prescribing to patients with predisposing factors for myopathy (eg: renal impairment, age ≥ 65, inadequate hypothyroid treatment)
- Increased risk of myopathy with concurrent use of fibrates, niacin (especially ≥ 1 gram per day), cyclosporine, lopinavir/ritonavir, or atazanavir/ritonavir
- Liver enzyme tests should be performed prior to rosuvastatin initiation due to risk of liver enzyme abnormalities
- Use caution with administering rosuvastatin in conjunction with anticoagulants due to risk of prolonging prothrombin time/INR. It is recommended to monitor INR until stable upon initiation or alteration of rosuvastatin therapy.
- Risk of proteinuria and hematuria
- Risk of increases in HbA1c and fasting glucose levels¹

Adverse Reactions:

- Serious adverse reactions: rhabdomyolysis with myoglobinuria, acute renal failure, myopathy, and liver enzyme abnormalities
- Most common adverse effects leading to treatment discontinuation during clinical trials (1.4% of patients): myalgia, abdominal pain, nausea
- Most common adverse reactions reported (incidence ≥ 2% of patients): headache (3.1% to 8.5%), myalgia (1.9% to 12.7%), abdominal pain (2.4%), asthenia (0.9% to 4.7%), nausea (up to 6.3%)
- Children treated with rosuvastatin had more frequent elevations in serum creatine phosphokinase (>10 x ULN) compared to children treated with placebo (4/130, 3% vs 0/46, 0%)^{1,2}

Interactions:

- Not significantly dependent on cytochrome P450 3A4 metabolism
- Substrate for certain transporter proteins (OATP1B1 and BCRP); therefore, increased rosuvastatin exposure (AUC) with concurrent use of cyclosporine (7-fold increase),

gemfibrozil (2-fold increase), and certain protease inhibitors (lopinavir/ritonavir, atazanavir/ritonavir (2 to 3-fold increase))

- Concurrent use of rosuvastatin with coumarin anticoagulants significantly increases INR
- Lipid-modifying doses of niacin (≥ 1 g/day) in combination with rosuvastatin enhances risk of skeletal muscle effects
- Simultaneous administration of aluminum and magnesium hydroxide significantly decreases rosuvastatin exposure by 54% (administration 2 hours apart decreases AUC only 22%)
- HMG-CoA reductase inhibitors known to increase risk of myopathy when concurrently used with fenofibrate; use caution with concurrent use
- Myopathy reported with coadministration of HMG-CoA reductase inhibitors with colchicine¹

Special Populations:

Pregnancy: teratogenic effects (pregnancy category X)

Nursing mothers: unknown whether rosuvastatin passes in human milk; advised to avoid rosuvastatin in nursing mothers due to another drug in this class known to pass into human breast milk

Pediatrics: same warnings and precautions as adults should be applied to patients ages 10 to 17; no controlled clinical trials performed on children less than 10 years of age

Geriatrics: no differences in effectiveness between geriatric and younger subjects; however, there is a higher risk of myopathy in elderly patients, so use rosuvastatin with caution

Renal impairment: dose adjust in patients with severe renal impairment not receiving dialysis

Hepatic impairment: contraindicated in patients with active liver disease¹

Costs and Monitoring:

Daily cost is \$6.40 for once a day dosing.

Lipid panel should be monitored 2 to 4 weeks after initiation and after dosage adjustments. Liver function must be monitored at baseline and when clinically indicated. High risks for abnormal liver function include large alcohol consumption and a history of chronic liver disease.²

How Supplied:

Tablet: 5 mg, 10 mg, 20 mg, 40 mg¹

Efficacy:

Hyperlipidemia and Mixed Dyslipidemia:

In a multicenter, double-blind, placebo-controlled, dose-ranging study, significant reduction in total-C, LDL-C, non-HDL-C, ApoB, and TG and increase in HDL-C were seen across all dose ranges of a single rosuvastatin daily dose for 6 weeks. In an active-controlled study, when compared to other HMG-CoA reductase inhibitors (atorvastatin, simvastatin, pravastatin), a more significant reduction in LDL-C was seen with rosuvastatin.¹

Heterozygous familial hypercholesterolemia:

In an active-controlled study, significant reductions from baseline in LDL-C seen in patients treated with 6 weeks of rosuvastatin 20 mg (-47% from baseline LDL-C) followed by 6 weeks of rosuvastatin 40 mg (-55% from baseline LDL-C).¹

Hypertriglyceridemia:

In a double-blind, placebo-controlled dose-response study, 6 weeks of a single daily dose (5 to 40 mg) rosuvastatin significantly reduced serum TG levels (median of -21% from baseline with 5 mg, -37% from baseline with 10 mg, -37% from baseline with 20 mg, and -43% from baseline with 40 mg) compared to changes in TG with the placebo (median of 1% from baseline).¹

Primary Dysbetalipoproteinemia:

In a randomized, multicenter, double-blind crossover study, rosuvastatin showed to reduce non HDL-C and circulating remnant lipoprotein levels when used in conjunction with the Therapeutic Lifestyle Change (TLC) diet.¹

Homozygous familial hypercholesterolemia:

In a dose-titration study, LDL-C was reduced by 22% from baseline when rosuvastatin dose was titrated from 20 mg to 40 mg after 6 weeks.¹

HeFH in pediatric patients:

In a double blind, randomized, multicenter, placebo-controlled study, the levels of LDL-C, total cholesterol, and ApoB levels were significantly reduced on patients given rosuvastatin. The LDL-C goal of < 100 mg/dL were achieved by 0% for placebo whereas the goals were met in subjects taking rosuvastatin: 5 mg (12% of subjects), 10 mg (41%), and 20 mg (41%).¹

Atherosclerosis progression:

In the Measuring Effects on Intima Media Thickness: an Evaluation Of Rosuvastatin 40 mg (METEOR) study, a double-blind, placebo-controlled clinical study, 984 patients were randomized to a 5:2 ratio of rosuvastatin or placebo. The rate of change of the mean maximum carotid intima-media thickness at 12 sites was determined by ultrasonograms. 52.1% of patients treated with rosuvastatin had an absence of disease progression compared to 37.7% in the placebo group.¹

Cardiovascular disease primary prevention:

In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, 17,802 men and women with no cardiovascular disease were assessed for the occurrence of major cardiovascular disease events. The subjects were randomly assigned to either the placebo (n=8901) or rosuvastatin 20 mg once daily (n=8901) group. The subjects were followed for two years, though the study terminated early due to meeting predefined stopping rules. The primary end point was the first-time occurrence of major CV events (nonfatal myocardial infarction, nonfatal stroke, or hospitalization due to unstable angina or arterial revascularization). Significant risk reductions of major CV events were seen in subjects given rosuvastatin (252 events in placebo group vs 142 events in rosuvastatin group) with statistically significant ($p < 0.001$) relative risk reduction of 44% and absolute risk reduction of 1.2%. No significant differences were seen between the placebo and rosuvastatin groups for death due to CV reasons or unstable angina. Rosuvastatin significantly reduced the risk of myocardial infarction (6 fatal and 62 nonfatal events in placebo group vs 9 fatal and 22 nonfatal events in rosuvastatin group) and risk of stroke (6 fatal and 58 nonfatal events in placebo group vs 3 fatal and 30 nonfatal events in rosuvastatin group).¹

Comparison between rosuvastatin and atorvastatin:

The Crestor® Athero Imaging Head to Head IVUS Study (SATURN), which was a 104-week, randomized, double-blind, parallel group, multi-center Phase IIIb study, compared the

efficacy between rosuvastatin 40 mg and atorvastatin 80 mg in treating atherosclerotic disease burden measured by intravascular ultrasound in coronary artery disease patients. After 104 weeks of therapy, patients treated with rosuvastatin had lower levels of LDL cholesterol than those treated with atorvastatin (62.6 vs. 70.2 mg/dL, $p < 0.001$) and higher levels of HDL cholesterol (50.4 vs. 48.6 mg/dL, $p = 0.01$). Although rosuvastatin achieved lower LDL levels and higher HDL levels, both groups had a similar degree of regression of percent atheroma volume, indicating their equal efficacy in achieving the primary endpoint.⁴

In a randomized trial, 120 patients with STEMI were assigned 1:1 to atorvastatin (80 mg/day) or rosuvastatin (20 mg/day). The lipid profile, values of oxidized-LDL, tumor necrosis factor receptor 1 and 2, interleukin-6, and hs-CRP were compared between the two groups after 4 weeks of therapy. Both groups had decreased levels of LDL-C, oxidized-LDL, hs-CRP, tumor necrosis factor receptor 1 and 2, and interleukin-6 according to baseline. The only difference between these two groups was a slight decrease in HDL-C in the atorvastatin group (-1.4 ± 8.9 mg/dL) versus an increase in HDL-C in the rosuvastatin group (2.0 ± 9.4 mg/dL, $p = 0.04$).⁵

In an open-label randomized trial in a high-risk Pakistani cohort, patients with type 2 diabetes, hypertension, myocardial infarction, or stroke were assigned to receive atorvastatin 10 mg HS or rosuvastatin 5 mg HS daily. After 6 weeks of therapy, patients receiving rosuvastatin had a greater absolute and percent reduction in serum LDL-C levels compared to patients receiving atorvastatin (0.96 mg/dL vs 0.54 mg/dL; $p = 0.011$ and 24.34% vs 13.66%; $p = 0.045$). Reduction in all other fractions of the lipid panel were equal between these two groups.⁶

Special circumstances for using rosuvastatin:

Rosuvastatin is only 10% metabolized, and it is primarily metabolized via the CYP2C9 pathway. On the other hand, atorvastatin is significantly metabolized by the liver, and its major metabolic pathway is via the CYP3A4 pathway. Due to these differences in metabolism of the drugs, rosuvastatin has less drug interactions than atorvastatin. Drug interactions that increase statin exposure can lead to a higher risk for rhabdomyolysis which may be life-threatening.^{2, 3}

Conclusions:

High intensity statins are the recommended agents for patients ≤ 75 years of age with clinical ASCVD, primary prevention in individuals ≥ 21 years of age with LDL-C ≥ 190 mg/dL, and primary prevention in individuals ages 40 to 75 with diabetes and estimated 10-year ASCVD risk of $\geq 7.5\%$. In addition, high-intensity statin therapy lowers LDL-C generally by at least 50%.⁷ For cases in which a high intensity statin is recommended but drug interactions with atorvastatin are of concern, rosuvastatin could serve as an equally efficacious and potentially safer alternative. Some studies have shown that rosuvastatin is more efficacious than is atorvastatin at lowering LDL-C and/or increasing HDL-C. However, there is a lack of head-to-head comparative studies between atorvastatin and rosuvastatin showing significant benefit of rosuvastatin over atorvastatin with regard to clinical outcomes, such as decreased morbidity and mortality. When the costs of the medications are taken into account, atorvastatin may be the preferred agent.

<u>Drug</u>	<u>Price per tablet</u>
Rosuvastatin 20 mg, 40 mg	\$6.40, \$6.40

Atorvastatin 40 mg, 80 mg	\$0.29, \$0.36
Pravastatin	<\$1
Simvastatin	<\$1
Fluvastatin	\$3.95

Recommendation:

Add rosuvastatin to the formulary as a reserve status for those needing high intensity statin therapy with nonresponse or significant drug-drug interactions with atorvastatin. The generic of this medication should be supplied starting July 2016. If the price of the medication decreases markedly, this medication may be reconsidered for uses other than for special circumstances.

References:

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 June 2015

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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: 7/24/15

Name of practitioner submitting the application: EFC

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)):

Information regarding new drug:

Therapeutic Classification	Antibiotic, Fluoroquinolone Ophth
Generic Name	maxifloxacin
Trade Name(s)	
Manufacturer(s)	
Dosage Form(s)	Ophth drops

Explain the pharmacological action or use of this drug:

fluoroquinolone

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

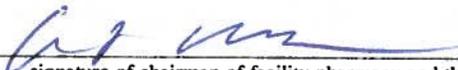
Frequently prescribed non-formulary

State which drugs this new drug would replace or supplement:

application is approved

OR

application is appropriate and complete


signature of chairman of facility pharmacy and therapeutics committee

signature of clinical/medical director or designee

Attachment A-2a

Moxifloxacin hydrochloride ophthalmic (Moxeza[®], Alcon; Vigamox[®], Alcon)

Classification: Antibiotic, Fluoroquinolone, Ophthalmic¹

Pharmacology:

Moxifloxacin is a fourth generation fluoroquinolone that has broad spectrum activity against Gram-positive, Gram-negative, anaerobes and atypical microorganisms. It works by inhibiting the bacteria's topoisomerase II (DNA gyrase) and topoisomerase IV. DNA gyrase is an essential enzyme for bacterial DNA involved in replication, transcription, and repair. Topoisomerase IV is an enzyme that has a key role in partitioning of the chromosomal DNA during bacterial cell division. Moxifloxacin is bactericidal.^{1,2}

Pharmacokinetics:

- Moxeza[®]: The following was evaluated in healthy adult subjects who administered twice-daily bilateral ophthalmic Moxeza[®] for 5 days: average steady-state AUC₀₋₁₂ was 8.17 ± 5.31 ng*h/mL; C_{max} was approximately 0.02% of that achieved with the oral formulation.¹
- Vigamox[®]: The following was evaluated in healthy adult subjects who administered three times daily bilateral ophthalmic Vigamox[®] for 5 days: average steady-state C_{max} (2.7 ng/mL) and estimated daily exposure AUC (45 ng*hr/mL) values were 1,600 and 1,000 times lower than the mean C_{max} and AUC of the oral formulation.³

Indications:

Moxifloxacin solution is used for the treatment of bacterial conjunctivitis caused by the following susceptible organisms:

Gram positive microorganisms: *Corynebacterium species*, *Enterococcus faecalis*, *Micrococcus luteus*, *Staphylococcus arlettae*, *S. aureus*, *S. capitis*, *S. epidermidis*, *S. haemolyticus*, *S. hominis*, *S. saprophyticus*, *S. warneri*, *Streptococcus mitis*, *S. pneumoniae*, *S. parasanguinis*,

Gram negative microorganisms: *Acinetobacter lwoffii*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Propionibacterium acnes*

Other microorganisms: *Chlamydia trachomatis*.¹

Dosage:

- Moxeza[®]: Instill 1 drop in the affected eye(s) 2 times daily for 7 days.¹
- Vigamox[®]: Instill 1 drop into affected eye(s) 3 times daily for 7 days.³

Contraindications

Patients with a history of hypersensitivity of moxifloxacin, to other quinolones, or to any of the components in this medication.³

Warnings and Precautions:

- Topical ophthalmic use only.
- Hypersensitivity and anaphylaxis have been reported with systemic use of moxifloxacin.
- Prolonged use may result in overgrowth of non-susceptible organisms, including fungi.
- Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis.¹

Adverse Reactions:

- 1% to 2%: eye irritation, pyrexia, and conjunctivitis.¹
- 1% to 6%: decreased visual acuity, dry eye, keratitis, ocular pruritus, subconjunctival hemorrhage and tearing.³

Interactions:

No known significant interactions.²

Special Populations:

Pregnancy: Risk factor category C

Nursing mothers: Moxifloxacin has not been measured in human milk but presumed to be excreted in human milk. Caution should be taken.

Pediatrics: There is no evidence that the use of ophthalmic moxifloxacin has any effect on weight bearing joints.

- Moxeza[®]: Safety and effectiveness in infants below 4 months of age have not been established.¹
- Vigamox[®]: Safety and effectiveness in infants below 1 year of age have not been established.³

Geriatrics: No overall differences in safety and effectiveness have been observed.

Renal impairment: No dose adjustment required.

Hepatic impairment: No dose adjustment required.¹

Costs:

Moxeza[®] ophthalmic solution 0.5% 3 mL: \$139.25

Generic moxifloxacin not available

Vigamox[®] ophthalmic solution 0.5% 3 mL: \$139.25

Generic moxifloxacin not available

Zymaxid[®] ophthalmic solution 0.5% 2.5 mL: \$138.45

Generic gatifloxacin ophthalmic solution 0.5% 2.5 mL: \$73.76

Ciloxan[®] ophthalmic solution 5 mL: \$108.65;

Generic ciprofloxacin ophthalmic solution 5 mL: \$2.66

Ciloxan[®] ophthalmic ointment 2.5 gm: \$175.25

Generic ciprofloxacin not available

Polytrim[®] ophthalmic solution 10 mL: \$60.20

Generic polymyxin B-trimethoprim ophthalmic solution 10 mL: \$3.63

How Supplied:

3 mL of sterile ophthalmic solution of moxifloxacin hydrochloride, 0.5% as base¹

Efficacy:**Common ocular pathogens:**

Staphylococcus aureus, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *viridans streptococci*, and *Moraxella catarrhalis* are the common bacterial causes of conjunctivitis.⁴ High incidence of *Pseudomonas* infections are seen in contact lens wearers.² Viral and allergic are other common causes of conjunctivitis.² Many cases of conjunctivitis are self-limiting.⁵ A randomized control trial of managing strategies of acute infective conjunctivitis showed that delayed antibiotic prescribing (3 days) may be effective in reducing antibiotic usage by about 50% with similar symptom control and reduced attendance for eye infection.⁵

Fourth generation fluoroquinolones:

Moxifloxacin and gatifloxacin offer the same coverage against gram-negative pathogens as earlier generation fluoroquinolones with enhanced activity against gram-positive pathogens and anaerobes. *In vivo* studies have shown a superior penetration into the eye than second generation fluoroquinolones. *In vitro* studies have shown that emergence of resistant isolates is less common with the fourth generation fluoroquinolones.⁶

Moxifloxacin versus ciprofloxacin:

Moxifloxacin is a fourth generation fluoroquinolone, giving it similar *in vitro* activity against gram-negative bacteria as ciprofloxacin but enhanced activity against gram-positive bacteria, including *S. aureus*.⁷

A study comparing ciprofloxacin, levofloxacin, and moxifloxacin for their *in vitro* effectiveness in treating experimental *S. aureus* keratitis found moxifloxacin retains greater activity in late therapy as well as having greater activity against the *MRSA* strains.⁷ These findings concur with previous *in vitro* studies comparing moxifloxacin to ciprofloxacin and levofloxacin.⁷

In a retrospective, cross-sectional study that evaluated resistance to ciprofloxacin among *MSSA* isolates from 1990 to 2001 found that ciprofloxacin resistance among *S. aureus* isolates has increased from 8% to 20.7% which is a 160% increase.⁸

Moxifloxacin versus gatifloxacin:

A study comparing the *in vitro* activity of gatifloxacin and moxifloxacin against ocular pathogens found gatifloxacin was at least as effective as moxifloxacin against the pathogens tested. Most of the gram + organisms have a similar MIC₉₀ except for *Strep viridans* in which gatifloxacin had significantly greater activity. Although both had activity against *Pseudomonas aeruginosa*, gatifloxacin also had greater activity against this pathogen as well (MIC₉₀ 1.28 mg/mL for gatifloxacin vs. 2.60 ng/mL for moxifloxacin). MIC₉₀ values for gatifloxacin against *Klebsiella pneumonia*, *Enterobacter aerogenes*, *Nocardia asteroides*, and *Mycobacterium chelonae* were approximately one fourth the values for moxifloxacin.⁹

A different study comparing the *in vitro* activity of the fourth generation fluoroquinolones found moxifloxacin to be more potent than gatifloxacin against gram-positive *MRSA* isolates. Bacterial endophthalmitis *MRSA* isolates were 87.5% susceptible to moxifloxacin vs. only 12.5% susceptible to gatifloxacin and 0% susceptible to ciprofloxacin. Otherwise, moxifloxacin and gatifloxacin had similar susceptibilities. Both gatifloxacin and moxifloxacin had better susceptibility to *Strep viridans* (both 100%) than ciprofloxacin (60%). Susceptibilities for gram negative pathogens were similar for ciprofloxacin, gatifloxacin and moxifloxacin.¹⁰

Both studies conclude that the fourth generation fluoroquinolones are highly effective against gram-positive and gram-negative ocular pathogens; however, moxifloxacin may be more effective against *MRSA* isolates. Additional clinical trials are necessary to determine superiority of moxifloxacin or gatifloxacin.

Moxifloxacin versus polymyxin B-trimethoprim

A single-blind, randomized controlled clinical trial of polymyxin B-trimethoprim compared with moxifloxacin for the treatment of acute conjunctivitis (55 *H. influenza*, 22 *S. pneumonia*,

4 *Moraxella catarrhalis*) in children aged 1 to 18 found that moxifloxacin is not superior to polymyxin B-trimethoprim. Cure rates identified by parents were 77% for moxifloxacin and 72% for polymyxin B-trimethoprim, clinical cure rates were 95% and 96% respectively and did not differ significantly between groups.¹¹

Conclusions:

Mild bacterial conjunctivitis is often self-limiting condition and ophthalmic antibiotics offer only marginal benefits in improving the clinical outcomes.⁵ However, antibiotics do provide an accelerated cure. Fluoroquinolones offer the best spectrum of activity for empiric therapy.⁴ Moxifloxacin, gatifloxacin, and ciprofloxacin all offer coverage against *Pseudomonas*; however, moxifloxacin and gatifloxacin have a higher susceptibility to *MSSA* bacteria due to increasing resistance to ciprofloxacin, which is the most common pathogen responsible for conjunctivitis. With regard to *MRSA* isolates, moxifloxacin may be preferred over other fluoroquinolones.¹⁰

If the bacterial conjunctivitis is occurring in a patient that does not wear contact lenses, other ophthalmic antibiotics can be used for inexpensive treatment unless *MRSA* is identified or suspected.¹²

Recommendation:

Add moxifloxacin to the formulary for bacterial conjunctivitis where *MRSA* is identified or suspected. Ciprofloxacin can still be used for contact wearers as long as *MRSA* is not suspected. In order to decrease the risk of resistance, only prescribe fluoroquinolones when necessary for *MRSA* or gram negatives are suspected.

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Attachment B

Medication Audit Criteria and Guidelines

Purpose of Laboratory and EKG Monitoring

This document was developed based on the premise that the laboratory tests and EKGs needed for prescribing psychotropic medications are apart from the laboratory tests obtained for the evaluation of the patient's general health status. The required laboratory tests and EKGs listed are specific for risk factors associated with that particular psychotropic medication. The required psychotropic medication laboratory and EKG screening does not substitute for a good history and physical and subsequent healthcare screening needed for the provision of good general medical care for the person who has become a psychiatric patient.

The specific laboratory tests and EKGs required for the use of psychotropic medication can be obtained from other treatment settings provided:

- The required laboratory tests and EKGs were obtained within 90 days prior to initiation of treatment.
- The actual values of the tests are documented in the chart. Other documentation shall include the date the lab work or EKG was obtained and the name of the facility.
- There are no intervening illnesses within those 90 days which would necessitate repeating the lab work or EKG.

The laboratory tests and EKGs listed in this document are minimum requirements. The clinician is encouraged to obtain any necessary lab work or EKG which he/she feels is clinically justified