DADS/DSHS EXECUTIVE FORMULARY COMMITTEE MINUTES
March 27, 2008

The Executive Formulary Committee convened on Friday, March 27, 2009 in Conference Room 240 - CO Building 2. The meeting was called to order by Dr. Matthews, Chair at 9:40 a.m.

Janet Adams, MSN, RN, CNS	Absent	Fred Bibus, M.D. (non-voting)	Absent
Emilie A. Becker, M.D.	√	Nina Muse, M.D. (non-voting)	Absent
Rosha Chadwick, R.Ph.	√	Kenny Dudley (non-voting)	Absent
Catherine S. Hall, Pharm.D.	√	Denice Geredine (non-voting)	Absent
Jeanna Heidel, Pharm.D.	√	Mike Maples (non-voting)	Absent
J. Brett Hood, M.D.	Absent	Bob Burnett (non-voting)	Absent
Jeff Matthews, M.D.	√	Julie McRae, MS, RN, CDDN (non-voting)	Absent
Connie Millhollon, RN,	Absent	Vacant DSHS Nursing Director (non-voting)	
Victoria Morgan, M.D.	√	Vacant Medical Director	
Ann L. Richards, Pharm.D.	√	Vacant Center Position	
Bill Race, M.D.	√	Vacant Center Position	
Robert L. Ward, D.O.	√	Vacant Center Position	

Guest Present: Debra Dandridge, Pharm.D., Resident, San Antonio State Hospital

Introductions

Dr. Victoria Morgan and Dr. Robert Ward were introduced as new members of the Committee. Dr. Morgan is representing a State School and Dr. Ward is a local authority practitioner.

Approval of Minutes of December 5, 2008

On a motion of Dr. Becker, seconded by Dr. Heidel, the minutes of the December 5th meeting were approved as previously distributed.

Adverse Drug Reaction Reports

The Executive Formulary Committee received numerous adverse drug reaction reports. In the first case, a 51 year old male was admitted to a psychiatric state hospital for treatment of depression. The patient was prescribed quetiapine (Seroquel®) 75 mg at bedtime and sertraline (Zoloft®) 100 mg in the morning at the time of admission. On day 5 of the admission, the dose of quetiapine was increased to 100 mg at bedtime and on day 6, the sertraline dose was increased to 150 mg in the morning. The following day, amitriptyline (Elavil®) 50 mg at bedtime was added to the medication regimen. The patient was tolerating his medication regimen and reported to his psychiatrist that he had previously been on sertraline 200 mg per day and had tolerated that dose. On day 13 of the admission, the sertraline dose was increased to 200 mg in the morning and the patient received this new dose on day 13 and 14. On day 14, the patient began to report sweating, trembling, visual phenomena, unsteadiness on feet, palpitations and rapid respirations. The patient was sent to a local medical hospital for the treatment of possible serotonin syndrome. At the medical hospital, the patient was administered fluids and lorazepam (Ativan®). The dose of sertraline was decreased to 100 mg daily and amitriptyline 50 mg and quetiapine 100 mg at bedtime were continued. The patient was sent back to the psychiatric facility. The patient was started on clonazepam (Klonopin®). The quetiapine and sertraline were tapered over time and then discontinued. Venlafaxine (Effexor®) XR was initiated and titrated to 112.5 mg/day. After this dose was reached, the patient was noted to have a subsequent episode of tachycardia and tremors with a heart rate of 103 BPM. The dose of venlafaxine XR was decreased to 75 mg and the amitriptyline was discontinued. The patient had no further symptoms of serotonin syndrome.

In the second adverse drug reaction report, a 47 year old male was admitted to a psychiatric facility with a history of psychosis, mental retardation, alcohol dependence, previous myocardial infarction, arthritis and hypertension. Prior to admission, his brother had taken him to an ER because he was poorly responsive and the patient reported that he may have taken "too much Haldol®." At the time of admission, the patient was prescribed thiamine 100 mg daily, folic acid 1 mg daily, multivitamin/minerals daily, amlodipine (Norvasc®) 10 mg daily, aspirin 81 mg daily, clonidine (Catapres®) patch 0.2 mg/24 hours to be replaced every 7 days and clonidine 0.1 mg twice daily. The haloperidol was subsequently reinitiated at 5 mg at bedtime and then increased to 5 mg twice a day. The patient was sent to the hospital medical clinic due to increased anxiety, profuse sweating, cold/clammy skin, total body tremors and increased confusion. At the clinic, the pulse oximeter was 91% on room air. An EKG revealed a T wave peak so cardiac enzymes were ordered. Levofloxacin (Levaquin®) was started empirically for a possible infection. The patient returned to the medical clinic two days later for a follow up. The blood cultures obtained on the first visit were negative; however, the patient had elevated WBC and liver function tests. Symptomatically the patient was agitated, confused and incoherent. The patient was sent to a medical hospital for further evaluation. At the medical hospital, the patient's blood pressure was 148/92, pulse 112, temperature 98.4 F, and respiration rate of 20 breaths/minute. Other pertinent findings include: EEG showed low voltage fast activity; leukocytosis (WBC 16,000); movements noted to be consistent with dystonia; CSF culture negative; UA negative; HIV negative; hepatitis panel negative; head CT showed no acute infarction, hemorrhage or mass – mild prominence of ventricular system and cortical sulci; and chest x-ray was normal. The CK was 2,609 U/L, CK-MB was 10.9 U/L, troponin-I was 0.06 ng/ml The haloperidol was discontinued and the dystonia improved with the addition of benztropine (Cogentin®) 2 mg three times a day. The levofloxacin was also discontinued due to lack of evidence for an infection. The patients WBC, CK, CK-MB, troponin-I, AST, ALT, T bilirubin decreased over time and the patient remained afebrile while at the medical hospital and did not have any lead pipe rigidity. In addition, the heart rate and blood pressure were variable, and the patient had tachycardia and was hypertensive. The patient was diagnosed as having acute dystonia and rhabdomyolysis secondary to haloperidol. The patient was sent back to the State Hospital with ziprasidone (Geodon®) 40 mg twice a day. The patients CPK increased to 2,376 U/L and then declined over time.

A 46 year old female on clozapine was discovered to have petechiae on limbs, torso and feet. The patient

refused treatment for two days. The patient was sent to an emergency room where she was admitted with a platelet count of 1,000 and hemoglobin of 7 g/dl. She was given irradiated platelets and red cells, which brought her hemoglobin up to 10.7 g/dl. Her white blood cell counts and differential remained normal during this event. Clozapine was held for five days while she was at the medical hospital and her platelets and hemoglobin normalized without further treatment.

A 38 year old male with a long history of psychiatric illness was admitted to a State Hospital. Several days after starting on isoniazid and pyridoxine, he exhibited symptoms of sedation, slow speech, increasing confusion and tachycardia. The isoniazid and pyridoxine were discontinued but the symptoms still persisted. Patient was transferred to a medical hospital where he was admitted with a diagnosis of acute delirium attributed to cyclobenzaprine (Flexeril®). The cyclobenzaprine and naproxen were discontinued and the patient was returned to the psychiatric facility where it was noted that his confusion had improved.

A 49 year old female was admitted to a State Hospital after a period of medication noncompliance and increase in psychiatric symptoms. The patient was reinitiated on her previous psychotropic regimen of quetiapine (Seroquel®) 300 mg three times a day and divalproex (Depakote®) ER 1,500 mg at bedtime for schizoaffective disorder. The patient was on levothyroxine (Synthroid®) 0.125 mg and atorvastatin (Lipitor®) 10 mg at bedtime. The patient also has a possible history of ovarian cancer noted in 2003 but the patient continues to refuse further evaluation and treatment. The day after admission, the patient's pertinent labs were: ANC 1.7, WBC 4.6 and platelets 302. On day 7 of hospitalization, the patient's valproic acid level was 120.4 mcg/ml. On day 14, the patient's labs were: ANC 1.5, WBC 4 and platelets 98. On day 23, the patient's valproic acid level was 78.4 mcg/ml, ANC 0.7 (nadir), WBC 3.3 (nadir) and platelets 85 (nadir). The divalproex ER was discontinued on day 23. Follow up lab work on day 27 showed an ANC 2.2, WBC 4.3 and platelets 122. The patient was discharged approximately one week later.

A State Hospital patient was transported to an emergency room due to ataxia, weakness in right arm and leg, increased confusion and sleeping all the time. The initial symptoms presented on 1/31/08 after a fall but the patient refused treatment for 2 weeks. The patient was referred to the emergency room for possible cerebrovascular accident (CVA). The patient returned to the State Hospital three days later after the CVA and meningitis were ruled out. The patient was diagnosed with hyponatremia secondary to psychogenic water drinking and put on fluid restrictions of 2,000 ml/day and sodium chloride 1,000 mg three times a day. However, the treatment team stated that the patient does not drink water excessively. The divalproex was decreased over time to 750 mg/day and then increased back to 1,500 mg/day. The sodium did rebound to within normal limits.

A 52 year old male taking divalproex/valproic acid for more than two years complained of stomach pain intermittently with no acute distress. The patient was treated with omeprazole (Prilosec®). Five days later, the patient complained of lower back pain and abdominal pain so the patient was treated for constipation. Complaints of vague stomach and back pain continued for four days. A comprehensive metabolic panel along with an amylase and lipase were ordered. The amylase was 540 IU/L and the lipase was 36 IU/L. The patient denied any nausea or vomiting, diarrhea or right abdominal pain. The divalproex was discontinued and the amylase has slowly declined.

A 51 year old female with multiple medical conditions including hypertension, diabetes, COPD and hyperlipidemia presented to the medical clinic with periorbital swelling and 2+ pitting edema in the lower extremities. The patient is being treated with enalapril (Vasotec®), gemfibrozil (Lopid®), omeprazole (Prilosec®), quetiapine (Seroquel®), albuterol/ipratropium (Combivent®) inhaler and albuterol. The physician prescribed hydrochlorothiazide/triamterene (Dyazide®) for the edema. In addition, the patient was having increasing respiratory difficulties and was referred to a pulmonologist. On a follow up visit nine days later, the patient was noted to have a congested cough and fluid bags below her eyelids. The

hydrochlorothiazide/triamterene was discontinued and furosemide (Lasix®) was started. Two days after this appointment, the patient was noted to have 2+ pitting edema, angioedema, skin below lower eyelids had fluid filled sacs and normal skin color. The patient denied any facial pain. Bumetanide (Bumex®) was started and gemfibrozil (Lopid®) was discontinued. On the next day, it was noted that the patient had some decrease in edema. The enalapril was discontinued. Further improved in her edema was observed.

A 33 year old female admitted to a psychiatric hospital for bipolar disorder experienced acute chronic kidney disease secondary to a combination of factors including recent NSAID use. On admission, the chronic kidney disease was Stage 2. Patient started on sulfamethoxazole/trimethoprim (Bactrim®) for an urinary tract infection. Later the patient complained of generalized pruritus. The patient was given diphenhydramine (Benadryl®) for itching and ibuprofen (Motrin®) for dental pain. Over a span of three days, the patient received 6 doses of ibuprofen 600 mg. The patient was started on clindamycin (Cleocin®) for a dental infection. The patient's BUN, serum creatinine, and potassium became elevated and the patient was diagnosed with chronic kidney disease Stage 5 (glomerular filtration rate 12 ml/min/1.73 m^2 with hyperkalemia, hyperalbuminemia and proteinuria). The patient was sent to a medical hospital for further treatment which included IV fluids, sliding scale insulin and nebulizer treatments. The patient's creatinine peaked at 5.4 mg/dl. This reaction was thought to be due to the ibuprofen.

On 4/10/08, a 53 year old male psychiatric patient with a long history of schizoaffective disorder with bipolar symptoms was transferred out to the emergency room for altered mental status including agitation and confusion, slurred speech, and possible dehydration. His medication at this time included lithium, olanzapine (Zyprexa®), clonazepam (Klonopin®), aspirin, metoprolol (Toprol®) and valsartan (Diovan®). At admission to the ER, he had a lithium level of 2.6 mEq/l. He was given IV fluids and lithium was discontinued. He was returned to the psychiatric facility with a diagnosis of lithium toxicity. His lithium level had decreased to 0.6 mEq/l but his speech was still slurred and the patient was still lethargic. He was returned to the ER on 4/15/08 with increased lethargy, minimally responsive and dehydrated. At this time, he was diagnosed with lower lobe pneumonia.

A 50 year old obese female with hypertension and diabetes had a baseline TSH of 2.25 mIU/L on 8/28/07. She was started on lithium for schizoaffective disorder on 5/12/08. On 5/19/08, the patient's TSH was 7.08 mIU/L. The lithium was discontinued and levothyroxine (Synthroid®) was started. On 7/16/08, the patient's TSH was 2.58 mIU/L.

A 48 year old female was admitted to a psychiatric hospital on an emergency detention warrant for suicidal thoughts and command hallucinations. She has a history of depression and suicidal ideation, but this worsened recently after starting a methylprednisolone (Medrol®) dose pack for bronchitis. At admission, the methylprednisolone was discontinued and her dose of aripiprazole (Abilify®) was increased. The hallucinations cleared and mood improved. The patient was discharged three days later.

A 59 year old male with schizoaffective disorder, bipolar type was admitted to a psychiatric facility with delusions and pressured speech. He was stabilized on medications and was doing well. The podiatrist recommended pregabalin (Lyrica®) for neuropathic pain (neuropathy). He was started on 50 mg twice a day on 10/22/08. On 10/28/08, it was noted that the patient had a complete return to mania with agitation, attempting to throw chairs, tangential, pressured and grandiose. The pregabalin was discontinued on 10/28/08. On 11/6/08, he was less manic, less pressured and less delusional.

A 47 year old male with a long history of psychiatric hospitalizations was started on oxcarbazepine (Trileptal®) on 6/10/08. On 6/17/08, the patient's sodium level was 125 mEq/l but he also has a history of excessive water intake. He was placed on fluid restrictions and on 6/20/08 his sodium was 127mEq/l. The oxcarbazepine was discontinued and on 6/25/08, his sodium level was 130 mEq/l.

A 31 year old male with a long history of schizophrenia is delusional with symptoms of low sodium including poor concentration, confusion, sedation and at least one episode of nausea/vomiting. The patient was placed on fluid restrictions on 3/3/08 for a sodium level of 131 mEq/l. Despite the fluid restriction, follow up labwork on 3/5/08 showed a sodium of 132 mEq/l and a chloride of 92 mEq/l. It was noted that the patient had not been drinking excessively and that he was taking oxcarbazepine (Trileptal®). The oxcarbazepine was tapered and on 4/22/08, the patient's sodium was 141 mEq/l and chloride 106 mEq/l. Additional labs were obtained on 6/24/08 which showed sodium 142 mEq/l and chloride 106 mEq/l.

A 40 year old male with bipolar disorder with psychotic features treated with oxcarbazepine (Trileptal®) had a sodium level of 125 mEq/l on 5/29/08. The patient was placed on fluid restriction at this time. On 5/30/08, a follow up sodium was 117 mEq/l. The oxcarbazepine was discontinued and the patient was transferred to a medical facility due to the hyponatremia. At the medical facility, the patient was treated with normal saline IV and fluid restriction. On 6/1/08 the sodium ranged from 121 to 136 mEq/l and an EKG indicated AV block. The hyponatremia was presumed to be due to oxcarbazepine and excessive fluid intake. On 6/3/08, the sodium level was 135 mEq/l and the fluid restriction was discontinued. On 6/12/08, the sodium was 141 mEq/l.

A 21 year old female was being treated with paliperidone (Invega®) for bipolar disorder with psychotic features. On 3/11/08, the patient complained that "her nipples were releasing milk." She also complained of bilateral breast tenderness. A prolactin level obtained on 3/12/08 was 22 ng/ml (WNL). However, five days later a follow up prolactin level was 64.6 ng/ml which was elevated. The paliperidone was discontinued and three days later the prolactin level declined to 29.6 ng/ml which further declined to 23.1 ng/ml eleven days later.

A 22 year old female admitted to psychiatric hospital on 9/11/08 for treatment of acute mania/bipolar disorder. She was receiving no other medication prior to admission, except emergency doses. On 9/12/08, she received stat haloperidol (Haldol®) and lorazepam (Ativan®) at 3:35 pm and was started on quetiapine (Seroquel®) 400 mg at bedtime. On 9/13/08, she received a second bedtime dose of quetiapine and shortly thereafter she fell in the bathroom. She was unresponsive, pupils sluggish to react, blood pressure 150/88 mm Hg, pulse 88, 12 respirations per minute, oxygen 95%, pale and diaphoretic. The patient was transported to an emergency room where she recovered spontaneously. It was suspected that the patient had orthostasis due to the lack of titration with the quetiapine dose. The quetiapine dose was lowered and titrated to 400 mg/day in divided doses without further incident.

A 43 year old female was admitted to a State Hospital on 10/10/08. The patient was suspected of probable noncompliance with her medications prior to admission. An EKG on 10/10/08 showed a normal QTc interval of 437 msec. All of her medications were restarted on 10/10/08, including quetiapine (Seroquel®) and cyclobenzaprine (Flexeril®). The EKG on 10/14/08 showed a QTc interval of 504 msec, which is markedly prolonged. The quetiapine was discontinued on 10/17/08. A repeat EKG obtained on 10/20/08 showed a QTc interval of 418 msec.

After discussing these adverse drug reactions, the Committee noted several concerns. The question was raised as to whether or not physicians and pharmacists are aware of the potential for serotonin syndrome to occur. The Committee discussed the best way to inform clinicians of the potential for serotonin syndrome. It was noted that the information on these adverse drug reactions would be included in the minutes. It was also suggested that a separate memo be distributed to the clinical/medical directors regarding the risk of serotonin syndrome in our patient population. Dr. Race raised the issue regarding the amount of polypharmacy that occurs in the treatment of our patients. In discussing the amount of polypharmacy, a question arose as to how much polypharmacy was created by the OD physician prescribing a medication that the attending physician was not aware of, so the attending physician

prescribes a similar drug. The Committee discussed the possibility of developing a Crystal Report that would compile a list of orders prescribed by a specific time frame by attending physician. This would allow the attending physician to review orders in a quick fashion. Other suggestions were to have a pop up mechanism in which the attending physician could be notified of any new orders on their patients when logging into the system. The Committee also expressed concern about the potential lithium toxicity with drugs that fall into the angiotensin II receptor blockers (ARB) category as was demonstrated with the patient on lithium and valsartan. It was recommended that a memo regarding this potential drug interaction with lithium be distributed to the field.

The Committee encourages facilities to continue to report adverse drug reactions to the Executive Formulary Committee

New Drug Applications

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

Carvedilol (Coreg®) - discussed by Dr. Hall

Carvedilol has a nonselective beta-adenoreceptor and alpha-adrenergic blocking activity. No intrinsic sympathomimetic activity has been documented. In hypertension, carvedilol reduces the following: cardiac output; exercise-or beta-agonist-induced tachycardia; reflex orthostatic tachycardia; peripheral vascular resistance; renal vascular resistance; plasma renin activity. Carvedilol also increases levels of atrial natriuretic peptide and is a vasodilator. In congestive heart failure (CHF), carvedilol decreases the following: heart rate; pulmonary capillary wedge pressure; pulmonary artery pressure; systemic vascular resistance; right arterial pressure (RAP). It increases the stroke volume index. Carvedilol is indicated for heart failure, left ventricular dysfunction following myocardial infarction, and hypertension. The immediate release carvedilol is available generically but the extended release (Coreg® CR) is not.

Following discussion, on motion of Dr. Beck, seconded by Ms. Chadwick, the request to add carvedilol immediate release (Coreg®) to the formulary was approved.

Guanfacine (Tenex®) - discussed by Dr. Dandridge

Guanfacine is a centrally acting antihypertensive which stimulates the alpha-2 adrenergic receptor thereby decreasing the output of the presynaptic norepinephrine neuron. The reduced sympathetic nerve impulses from the vasomotor center to the heart and blood vessels results in a slight reduction in heart rate (5 beats/minute) and peripheral vascular resistance. Other alpha-2 adrenergic agonists such as clonidine (Catapres®) have shown beneficial effects as non-first line agents in children with Attention Deficit Hyperactivity Disorder (ADHD). Guanfacine, an agent similar to clonidine may be an alternative based on a longer half-life, decreased sedative and hypotensive properties, and more selective binding profile. It appears that alpha-2 adrenergic agonist may exert psychoactive effects via direct effects on the noradrenergic neurotransmitter system, indirectly affecting serotonin and dopamine transmission. In addition, alpha-2 adrenergic agents may decrease tics in children with ADHD and tic disorders. Guanfacine is indicated for the treatment of hypertension either alone or in combination with other antihypertensives. Guanfacine is used off-label for attention deficit hyperactivity disorder and Tourette's syndrome (children/adolescents). For the off-label use in ADHD the initial dose is 0.5 mg/day with increases of 0.5 mg every 3 to 4 days or 0.25 to 0.5 mg every 5 to 7 days as needed or tolerated. For Tourette's Syndrome in children/adolescents the dose is 0.5 mg orally once daily titrated slowly based on response and adverse reactions to a maximum dose of 4 mg/day in 3 divided doses.

Following discussion, on motion of Dr. Ward, seconded by Dr. Beck, the request to add guanfacine (Tenex®) to the formulary was approved. It was also recommended that guanfacine be listed in the Drug Formulary under ADHD.

The audit criteria for guanfacine will need to be developed.

Linezolid (Zyvox®) - presented by Dr. Richards (developed by Regina Tabor)

Linezolid is a synthetic antibacterial agent. It inhibits bacterial protein synthesis by binding to bacterial 23S ribosomal RNA of the 50S subunit. This prevents the formation of a functional 70S initiation complex that is essential for the bacterial translation process. Linezolid is bacteriostatic against enterococci and staphylococci and bactericidal against most strains of streptococci. It is indicated for vancomycin-resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia. It is also indicated for nosocomial pneumonia, complicated skin and skin structure infections, and community acquired pneumonia including concurrent bacteremia. For a non-FDA approved indication, linezolid is used in the treatment of mycobacterial infections. It has been used as a third-line regimen for the treatment of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB). Patients on linezolid must have weekly CBC and platelet counts and those on it for 3 months or more should have their visual function tested on a routine basis.

Following discussion, on motion of Dr. Morgan, seconded by Dr. Heidel, the request to add linezolid (Zyvox®) to the formulary was approved as a reserve drug with the criteria of: Patients at TCID or in consultation with an expert in infectious disease.

Possible TAC Change

The Committee is still pursuing the option of changing the TAC regarding the requirements for the completion of an evaluation for movement disorders for typical and atypical antipsychotics. At this time, a Work Group has not been formed.

FDA Alerts

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

> The FDA notified healthcare professionals that the makers of clopidogrel (Plavix®) have agreed to work with the FDA to conduct studies to obtain additional information that will allow a better understanding and characterization of the effects of genetic factors and other drugs (especially proton pump inhibitors (PPIs)) on the effectiveness of clopidogrel. The FDA is aware of published reports that clopidogrel is less effective in some patients than it is in others. Differences in effectiveness may be due to genetic differences in the way the body metabolizes clopidogrel or that using certain other drugs with clopidogrel can interfere with how the body metabolizes clopidogrel. Healthcare providers should continue to prescribe and patients should continue to take clopidogrel as directed, because clopidogrel has demonstrated benefits in preventing blood clots that could lead to a heart attack or stroke. Healthcare providers should re-evaluate the need for starting or continuing treatment with a PPI, including omeprazole (Prilosec®) OTC, in patients taking clopidogrel.
>
> The manufacturers of metoclopramide (Reglan®), a drug used to treat gastrointestinal disorders,

must add a boxed warning to their drug labels about the risk of its long-term or high-dose use. Chronic use of metoclopramide has been linked to tardive dyskinesia, which may include involuntary and repetitive movements of the body, even after the drug is no longer taken. These symptoms are rarely reversible and there is no known treatment.

Updated clinical data has determined that treatment with zonisamide (Zonegran®), indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy, can cause metabolic acidosis in some patients. Patients with predisposing conditions or therapies may be at greater risk for developing metabolic acidosis and the risk of zonisamide-induced metabolic acidosis appears to be more frequent and severe in younger patients. The FDA recommends that healthcare professionals measure serum bicarbonate before starting treatment and periodically during treatment with zonisamide, even in the absence of symptoms.

Transdermal drug patches with metallic backings may place a patient at risk of burns to the skin if the patch is worn during an MRI scan. Information regarding the content of the backing will be included in the labeling. Until definitive information regarding the content of the patch is available, patients with patches should remove and dispose of the patch before the MRI and replace the patch after the MRI scan.

All SSRIs and SNRIs have added a class warning regarding the development of serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions. The warning basically states that the development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists.

Propoxyphene (Darvon®) FDA Panel Recommendation

At a joint meeting of FDA's Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committees on January 30, 2009, advisors voted 14 to 12 that propoxyphene and propoxyphene-containing products should be removed from the market. Propoxyphene and propoxyphene combinations are used for the treatment of mild-to-moderate acute pain.

In 2006, Public Citizen filed a request that the FDA begin a phased removal of these agents from the market. Dr. Sidney M. Wolfe, MD, Director of the Health Research Group at Public Citizen, discussed the FDA's efficacy review of this agent, stating, "The FDA review stands on its own merits and, in essence, finds that a) the addition of propoxyphene to acetaminophen does not result in a statistically significant improvement in pain relief compared with acetaminophen alone and b) that propoxyphene alone has only 'weak analgesic effects." Wolfe also pointed to Florida medical examiner data and information from the Drug Abuse Warning Network (DAWN), which collects data from drug-related visits to emergency rooms and drug-related deaths investigated by medical examiners and coroners, to suggest that propoxyphene has been associated with numerous deaths. Wolfe concluded, "Propoxyphene has one of the most unfavorable benefit-to-risk ratios I have ever seen for a drug. This committee will hopefully agree with this and recommend the beginning of a two-year phased withdrawal of these products."

In a presentation on behalf of the FDA, Joann H. Lee, Pharm.D., Division of Pharmacovigilance II, and Fatmatta Kuyateh, M.D., M.S., Division of Epidemiology discussed their findings from a literature review and items reported through Adverse Event Reporting System (AERS). Lee and Kuyateh found there was potential association between the agent and the adverse event in some cases, whereas no causal

relationship could be established in others. The potential relationship between propoxyphene and cardiotoxicity could likewise not be established. They concluded that "despite current propoxyphene label warnings, narcotic pain relievers and CNS-related drugs continue to be prescribed and used with propoxyphene-containing products, resulting in accidental and intentional deaths."

The FDA has not yet reached a decision regarding whether these products will be removed from the market. Propoxyphene and propoxyphene combination products are not on the Formulary and the Executive Formulary Committee continues to discourage their use.

Children & Adolescent Treatment of Behavior Emergencies Statement in the Formulary

The Committee developed recommendations for the treatment of behavioral emergencies with intramuscular short-acting agents based on survey data obtained from the field. Individuals from the field expressed concern about the interpretation of the information. Therefore, the following statement was added to the recommended dose table in the Formulary:

> "The following doses are for recommendation only and were obtained from a survey of use that was completed by practitioners that treat this population within our agency. These doses are not based on any literature support and are to be used for general guidelines."

The Committee approved the statement as written.

Psychotropic Consent List

Dr. Richards presented the psychotropic consent list for review by the Committee. Based on Dr. Becker's comments at a previous meeting, the following statement was added to the document:

> The classification of psychotropic medication is fairly standard but medications can be used for treatment of illnesses that would be considered listed under a different classification. For example, some medications listed under antipsychotics maybe used as a mood stabilizer.

The following changes were made to the psychotropic consent list:

- Add desvenlafaxine (Pristiq®) nonformulary to the antidepressant list
- Changed nefazodone (Serzone®) to nonformulary
- Add selegiline (Emsam®) to the monoamine oxidase inhibitor list
- Add lisdexamfetamine (Vyvanse®) nonformulary to the stimulant list
- Add methamphetamine (Desoxyn®) nonformulary to the stimulant list
- Add methylphenidate patch (Daytrana®) nonformulary to the stimulant list
- Add the trade name Metadate CD to the methylphenidate listing
- Remove nonformulary to the guanfacine listing

On a recommendation of Dr. Heidel, seconded by Dr. Morgan the Psychotropic Consent list was approved. See Attachment B.

Quarterly Non-Formulary Drug Justification Report

In reviewing the second quarter's non-formulary drug purchases, it was noted that drugs added at this meeting: guanfacine (Tenex®), linezolid (Zyvox®) and carvedilol (Coreg®) were listed in the top 30 agents. The Committee will address the addition of other top non-formulary users, such as, cetirizine (Zyrtec®) and levalbuterol (Xopenex®) in the near future.

Drug Formulary Sectional Review- Cardiovascular Agents

The review was not available for the meeting.

Sectional Review for Next Meeting

A decision regarding the next sectional review will be made at a later date.

Other Issues

Dr. Race reported that a bill was submitted to the legislature regarding the use of psychotropics in children less than 11 years old. In this bill, the use of psychotropic medication would be restricted to only those drugs that are FDA approved in this patient population. Since the agency is following this bill, the Committee decided to adopt a "wait and see" approach to monitoring this bill.

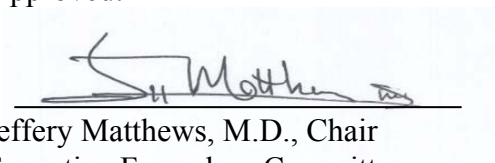
Next Meeting Date

The next meeting was scheduled for June 12, 2009.

Adjourn

There being no further business, the meeting was adjourned at 1:20 p.m.

Approved:



Jeffery Matthews, M.D., Chair
Executive Formulary Committee

Attachments
- Attachment A – New Drug Applications
- Attachment B – Psychotropic Consent List

Minutes Prepared by:
Ann L. Richards, Pharm.D., BCPP

Carvedilol

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: 03-27-09

Name of practitioner submitting the application: Ann Richards, Pharm.D. (for 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)): San Antonio State Hospital

Information regarding new drug:

Therapeutic Classification	Beta-Blocker with Alpha-Blocking Activity
Generic Name	Carvedilol
Trade Name(s)	Coreg
Manufacturer(s)	Generic
Dosage Form(s)	

Explain the pharmacological action or use of this drug:
See monograph

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

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

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☐ application is approved

Ann L. Richards

signature of chairman of facility pharmacy and therapeutics committee

OR

☐ application is appropriate and complete

signature of clinical/medical director or designee

(Coreg)

Carvedilol Extended-Release
(Coreg CR)

Classification: Beta-Blocker with Alpha-Blocking Activity

Pharmacology:

Carvedilol has nonselective beta-adrenoreceptor and alpha-adrenergic blocking activity. No intrinsic sympathomimetic activity has been documented.

In hypertension, carvedilol reduces the following: cardiac output; exercise-or beta-agonist-induced tachycardia; reflex orthostatic tachycardia; peripheral vascular resistance; renal vascular resistance; plasma renin activity. Carvedilol also increases levels of atrial natriuretic peptide and is a vasodilator.

In congestive heart failure (CHF), carvedilol decreases the following: heart rate; pulmonary capillary wedge pressure; pulmonary artery pressure; systemic vascular resistance; right arterial pressure (RAP). It increases the stroke volume index.

Pharmacokinetics:

Absorption: Carvedilol is rapidly and extensively absorbed following oral administration. It undergoes a significant degree of first-pass metabolism and the absolute bioavailability ranges from 25-35%. Food slows the rate, but not the extent, of bioavailability. Taking carvedilol with food should minimize the risk of orthostatic hypotension.

Distribution: Carvedilol is a basic, lipophilic compound whose steady-state volume of distribution equals approximately 115 L, which indicates substantial distribution into the extravascular tissues. It is more than 98% bound to plasma proteins, mainly albumin.

Metabolism: Carvedilol is extensively metabolized by oxidation (phase I), primarily via CYP2D6 and CYP2C9. Demethylation and hydroxylation at the phenol ring produce three active metabolites with B-receptor blocking activity. Based on preclinical studies, one of these metabolites (4'hydroxyphenyl) is an approximately 13 times more potent beta-blocker than the parent drug. Compared to carvedilol, the three active metabolites exhibit weak vasodilating activity. Carvedilol's oxidative metabolites are conjugated via glucuronidation and sulfation (phase II).

Elimination: Following oral administration, the apparent mean terminal elimination half-life of carvedilol ranges from seven to ten hours. Carvedilol's metabolites are primarily excreted via the bile into the feces. One study showed that less than 2% of the dose was excreted unchanged in the urine.

Indications:

Carvedilol and carvedilol extended-release (Coreg CR) are indicated for heart failure, left ventricular dysfunction following myocardial infarction, and hypertension.

Dosage and Administration:

Carvedilol should be taken with food to slow the rate of absorption and reduce orthostasis.

Heart Failure: Fluid retention should be minimized before carvedilol's initiation. The recommended starting dose is 3.125 mg po BID for 2 weeks; if tolerated, the dose can be doubled every two weeks up to 25 mg po BID. A maximum dose of 50 mg po BID has been given to patients weighing over 85 kg who have mild-to moderate heart failure.

Extended release: Initial dose is 10 mg once daily for two weeks; if the dose is tolerated, increase dose to 20 mg, 40 mg, and 80 mg over successive intervals of at least two weeks.

Left Ventricular Dysfunction following Myocardial Infarction: Carvedilol should be initiated only after the patient is hemodynamically stable and fluid retention has been minimized. The initial dose is 3.125-6.25 mg BID; if tolerated, after three to ten days, increase dosage to 12.5 mg BID, then again to the target dose of 25 mg BID.

Extended release**:** Initial dose is 20 mg once daily; increase dosage incrementally at intervals of 3 to 10 days to a target dose of 80 mg once daily.

Hypertension: Initial dose is 6.25 mg twice daily; if tolerated, dose should be maintained for 1-2 weeks, then increased to 12.5 mg twice daily. Dosage may be increased to a maximum of 25 mg twice daily after 1-2 weeks; maximum dose is 50 mg/day.

Extended release: Initial 20 mg once daily, if tolerated dose should be maintained for 1-2 weeks then increased to 40 mg once daily if necessary; maximum dose is 80 mg once daily.

Contraindications:

COREG is contraindicated in the following conditions:

- Bronchial asthma or related bronchospastic conditions. Deaths from status asthmaticus have been reported following single doses of COREG.
- Second- or third-degree AV block
- Sick sinus syndrome
- Severe bradycardia (unless a permanent pacemaker is in place)
- Patients with cardiogenic shock or who have decompensated heart failure requiring the use of intravenous inotropic therapy. Such patients should first be weaned from intravenous therapy before initiating COREG.
- Patients with severe hepatic impairment
- Patients with a history of a serious hypersensitivity reaction (e.g., Stevens-Johnson syndrome, anaphylactic reaction, angioedema) to carvedilol, any of the components of COREG, or to COREG CR

Warnings/Precautions and Adverse Reactions:

Cessation of therapy: Patients who have coronary artery disease (CAD) should be advised against abrupt discontinuation of therapy with Coreg. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with B-blockers. Coreg should be discontinued over one to two weeks whenever possible; because CAD is common and may be unrecognized, it may be prudent not to discontinue therapy with Coreg abruptly even in patients treated only for hypertension or heart failure.

Dizziness: In patients with mild-moderate heart failure, dizziness occurred in 32% of patients taking Coreg compared to 19% of patients on placebo. In patients with severe heart failure, dizziness occurred in 24% of patients taking Coreg compared to 17% of patients taking placebo.

Bradycardia: If pulse rate drops below 55 beats/minute, the dosage should be reduced.
In clinical trials, Coreg caused bradycardia in about 9% of heart-failure patients, 6.5% of myocardial patients with left ventricular dysfunction, and 2% of hypertensive patients.

Hypotension: Risk is highest during up-titration. Starting with a low dose, administration with food, and gradual up-titration should decrease the likelihood of syncope or excessive hypotension.

In clinical trials of mild-to-moderate heart failure, hypotension and postural hypotension occurred in 9.7% and syncope in 3.4% of patients receiving Coreg compared to 3.6% and 2.5% of placebo patients, respectively. In a clinical trial conducted in patients with severe heart failure (COPERNICUS), hypotension and postural hypotension occurred in 15.1% and syncope in 2.9% of heart failure patients receiving Coreg compared to 8.7% and 2.3% of placebo patients, respectively. These events led to discontinuation in 1.1% of patients receiving Coreg, compared to 0.8% of placebo patients.

In the CAPRICORN study of survivors of an acute myocardial infarction, hypotension or postural hypotension occurred in 20.2% of patients receiving Coreg compared to 12.6% of patients receiving placebo. Syncope was reported in 3.9% and 1.9% of patients, respectively. These events led to discontinuation of therapy in 2.5% of patients receiving Coreg, compared to 0.2% of placebo patients.

In hypertensive patients, postural hypotension occurred in 1.8% and syncope in 0.1% of patients, mainly following the initial dose or at the time of dose increase. These events led to discontinuation of therapy in 1% of patients treated with carvedilol (versus 0 treated with placebo).

Heart Failure/Fluid Retention: Worsening heart failure or fluid retention may occur during the up-titration of carvedilol. If this occurs, diuretics should be increased and the carvedilol dose should not be advanced until clinical stability is achieved. It is occasionally necessary to lower the carvedilol dose or temporarily discontinue it; these episodes do not preclude subsequent successful titration of, or a favorable response to, carvedilol.

In a the first 3 months of a placebo-controlled trial of patients with severe heart failure (COPERNICUS), worsening heart failure was reported to a similar degree with carvedilol and with placebo. Beyond three months, worsening heart failure was reported less frequently in patients treated with carvedilol than with placebo. Worsening heart failure observed during long-term therapy is more likely to be related to the patients' underlying disease than to treatment with carvedilol.

Non-allergic Bronchospasm

Patients with bronchospastic disease (e.g., chronic bronchitis and emphysema) should, in general, not receive B-blockers; however, Coreg may be used with caution in patients who cannot tolerate or who do not respond to other antihypertensive agents. To minimize the inhibition of endogenous or exogenous B-agonists, the smallest effective dose should be used. The dose should be lowered if any evidence of bronchospasm is observed during up-titration. In clinical trials of patients with heart failure, patients with bronchospastic disease were enrolled if their bronchospastic condition did not require treatment with oral or inhaled medication.

Glycemic Control in Type 2 Diabetes

In general, beta-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia.

In heart failure patients with diabetes, carvedilol may lead to worsening hyperglycemia. Blood glucose should be monitored when carvedilol dosing is initiated, adjusted, or discontinued. Studies designed to examine the effects of carvedilol on glycemic control in patients with diabetes and heat failure have not been conducted.

In a study that examined carvedilol's effect on glycemic control in patients with mild-to-moderate hypertension and well-controlled type 2 diabetes, carvedilol had no adverse effect on glycemic control (based on HbA1c measurements).

Monitoring Parameters: Heart rate, blood pressure (base need for dosage increase on trough blood pressure measurements and for tolerance on standing systolic pressure 1 hour after dosing); renal studies, liver function. In patients with renal dysfunction, monitor during dosage titration.

Drug Interactions

Increased Effect/Toxicity: Amiodarone and fluconazole inhibit CYP 2C9, thus increasing the levels/effects of carvedilol. Other CYP 2C9 inhibitors include delavirdine, gemfibrozil, ketoconazole, nicardipine, NSAIDs, sulfonamides, and tolbutamide.

CYP 2D6 inhibitors may also increase the levels/effects of carvedilol. Example inhibitors include chlorpromazine, delavirdine, fluoxetine, miconazole, paroxetine, pergolide, quinidine, quinine, ritonavir, and ropinirole.

Cimetidine may increase serum levels/effects of carvedilol. SSRI's may decrease the

metabolism of carvedilol.
Fentanyl may increase the bradycardic and hypotensive effects of beta-blockers. Calcium channel blockers may add to carvedilol's hypotensive effect.

Carvedilol may increase the levels/effects of cyclosporine and digoxin.

Decreased Effect: CYP 2C9 inducers may decrease the levels/effects of carvedilol; example inducers include carbamazepine, phenobarbital, phenytoin, rifampin, rifapentine, and secobarbital.

Concurrent use of amphetamines, NSAID's, or salicylates can lead to decreased antihypertensive effect of beta-blockers. Beta-blockers may counteract the desired effects of beta-agonists.

Cost Comparison of Carvedilol versus Coreg CR

Carvedilol strength*	AWP price per 100 tabs	AWP price per tab	Purchase price per 100 tabs	Purchase price per tab
12.5 mg	$211.31	$2.11	$4.36	$0.0436
25 mg	$211.31	$2.11	$4.36	$0.0436
50 mg	$211.31	$2.11	$4.36	$0.0436

*CARA

Coreg CR strength	AWP price per #30	AWP price per capsule	Purchase price per #30	Purchase price per capsule
20 mg	$136.61	$4.55	$104.88	$3.50
40 mg	$136.61	$4.55	$104.88	$3.50
80 mg	$136.61	$4.55	$104.88	$3.50

Efficacy:

Heart Failure: COMET (*C*arvedilol *O*r *M*etoprolol *E*uropean *T*rial) was a double-blind trial in which 3,029 patients with NYHA class II-IV heart failure (left ventricular ejection fraction $\leq$ 35%) were randomized to receive either carvedilol at a target dose of 25 mg BID or immediate-release metoprolol tartrate at a target dose of 50 mg BID. Approximately 96% of the patients had NYHA class II or III heart failure, mean age was approximately 62 years, 80% were male, and the mean left ventricular ejection fraction at baseline was 26%. Concomitant treatment included diuretics (99%), ACE inhibitors (91%), digitalis (59%), aldosterone antagonists (11%), and "statin" lipid-lowering agents (21%). The average duration of follow-up was 4.8 years and the mean dose of carvedilol was 42 mg per day.

COMET's two primary end points were all-cause mortality and the composite of death plus hospitalization for any reason. All-cause mortality was 34% in the patients treated with carvedilol and 40% in the patients treated with immediate-release metoprolol ($p = 0.0017$; hazard ratio = 0.83, 95% CI = 0.74-0.93). Reduction in cardiovascular death primarily accounted for the drop in mortality; estimated mean survival was 8.0 years with carvedilol and 6.6 years with immediate-release metoprolol. There was no significant difference between the two groups with respect to the composite end point ($p = 0.122$). The COMET trial extends the time over which carvedilol benefits survival in heart failure; however, it is not evidence that carvedilol improves

outcomes over the extended-release formulation of metoprolol (TOPROL-XL®)
The COPERNICUS trial was conducted in 2,289 patients with severe heart failure living in Eastern and Western Europe, the United States, Israel, and Canada. Severe heart failure was defined as heart failure at rest or with minimal exertion and a left ventricular ejection fraction < 25% (mean 20%) despite therapy with digitalis (66%), diuretics (99%), and ACE inhibitors (89%). In this double-blind trial, patients were randomized to placebo or carvedilol; carvedilol was titrated from 3.125 mg po BID to the maximum tolerated dose or up to 25 mg po BID over a minimum of six weeks.

COPERNICUS' primary end point was all-cause mortality. A data monitoring committee followed the developing trial data. The trial was stopped after a median follow-up of ten months because of a 35% reduction in mortality (from 19.7% per patient year on placebo to 12.8% on carvedilol, hazard ratio 0.65, 95% CI 0.52-0.81, p = 0.0014, adjusted). Hospitalizations were also assessed. Fewer patients on carvedilol than on placebo were hospitalized for any reason (372 versus 432, p = 0.0029), for cardiovascular reasons (246 versus 314, p = 0.0003), or for worsening heart failure (198 versus 268, p = 0.0001). Carvedilol's benefits extended to all subgroups examined, including men and women, elderly and non-elderly, blacks and non-blacks, and diabetics and non-diabetics.

Carvedilol extended-release (Coreg CR) was approved for use in heart failure based on pharmacokinetic and pharmacodynamic (beta-1 blockade) equivalence with Coreg.

The COMPARE trial was presented at the Heart Failure Society of America 2008 Scientific Meeting. It showed that, in patients with stable, chronic, mild to severe ischemic or non-ischemic heart failure and an LVEF ≤ 40%, once-a-day carvedilol (Coreg-CR) is "non-inferior" to the twice-daily version. The primary end-point of this 24-week, randomized, double-blind,"double-dummy" trial was change in LV end-systolic-volume index (LVESVI); secondary end points were left ventricular ejection fraction (LVEF) and B-type natriuretic peptide (BNP).

Echocardiographic, Hemodynamic, and Biomarker Changes for 253 patients who completed the COMPARE trial, CR vs IR Carvedilol

End point	**CR carvedilol, n = 125**	**IR carvedilol, n = 128**	**p**
Δ in LVESVI (ml/m^2)	-20.8	-18.4	0.98
Δ in LVEF (% points)	+8	+8	NS
Δ in systolic BP (mm Hg)	+7.5	+1.4	0.0005
Δ in BNP (pg/mL)	-96.7	-102.8	NS

Left Ventricular Dysfunction Following Myocardial Infarction: The CAPRICORN study was a double-blind trial that compared carvedilol and placebo in 1,959 patients who had experienced a MI within the last 21 days and who had a left ventricular ejection fraction ≤ 40%, with (47%) or without symptoms of heart failure. Background treatment included ACE inhibitors or angiotensin receptor blockers (97%), anticoagulants (20%), lipid-lowering agents (23%), and

diuretics (34%). Patients' average age was 63 years, 74% male, 95% Caucasian, mean blood pressure 121/74 mm HG, 22% with diabetes, and 54% with a history of hypertension. Mean dose of carvedilol was 20 mg po BID, mean duration of follow-up was 15 months.

Nearly all deaths were cardiovascular. All-cause mortality was 15% in the placebo group and 12% in the carvedilol group, which indicates a 23% risk reduction in patients treated with carvedilol (95% CI 2-40%, p = 0.03). Compared to patients treated with placebo, patients treated with carvedilol demonstrated a 40% risk reduction in fatal or non-fatal myocardial infarction (95% CI 11%-60%, p = 0.01). The end point of total mortality and all-cause hospitalization did not show a significant improvement.

Carvedilol extended-release (Coreg CR) was approved for use in left ventricular dysfunction based on pharmacokinetic and pharmacodynamic (beta-1 blockade) equivalence with Coreg.

Hypertension

Carvedilol has been studied in 2 placebo-controlled trials utilizing dosing ranging from 6.25 mg BID to 25 mg BID. The starting dose utilized in the trials did not exceed 6.25 mg BID. The peak effect was noted after 1 to 2 hours. Dose-related reductions in blood pressure are accompanied by dose-related increases in adverse effects. Blood pressure response was smaller in black than non-black patients. No age or gender-related changes in response were noted.

Table 1: Change in heart rate and blood pressure with carvedilol immediate release

Dose	Change in Heart Rate	Reduction in SBP/DBP at 12-Hour Trough (mmHg)
12.5 mg BID	N/A	-7.5/-3.5
25 mg BID	↓ by 7.5 beats per minute	-9/-5.5

Carvedilol's antihypertensive effect has also been compared to three other B-blockers: atenolol, labetalol and metoprolol. Atenolol was compared with carvediol in a randomized, double-blind, double-dummy parallel-group study of 258 patients with mild to moderate essential hypertension (sitting or standing diastolic blood pressure (DBP) 95-115mmHg). Patients were randomized to carvedilol 12.5mg daily, atenolol 50mg daily or placebo. Medication was titrated up weekly if DBP was >90 until the DBP was <80mmHg or the SBP was <120mmHg. Mean age was 54.9 years. Thirteen percent of carvedilol patients were maintained on 25mg daily and 77% were maintained on 50mg daily. After an average of 25 to 29 days, carvedilol and atenolol demonstrated statistically significant reductions in blood pressure compared to placebo. However, atenolol demonstrated significantly greater reductions in blood pressure compared to carvedilol. (Data on file, 095C1109)

Table 2: Change in sitting and standing DBP of placebo, atenolol and carvedilol

Drug	Change in sitting	Change in standing

	DBP (mmHg)	DBP (mmHg)
Placebo	-3.5	-2.3
Carvedilol (12.5-50mg daily)	-6.4	-7.5
Atenolol (50-100mg daily)	-11.3	-9.9

Carvedilol was compared to labetalol in a randomized, placebo-controlled, double-blind, parallel-group study of 264 patients (Mean age 54 years). Patients with mild-moderate essential hypertension were recruited (sitting or standing DBP 95 to 115mmHg). Patients were randomized to carvedilol 6.25 to 25mg BID, labetalol 100 to 400mg BID, or placebo for 8 weeks. Carvedilol and labetalol demonstrated statistically significant reductions in blood pressure compared to placebo but not when compared to each other (Data on file, 028 (B104).

Table 3: Change in sitting DBP after 8 week treatment with placebo, carvedilol, labetalol

Drug	Change in sitting DBP (mmHg)
Placebo	-4.1
Carvedilol (6.25-25mg BID)	-6.3
Labetalol (100-400mg BID)	-8.6

Hypertension with Type 2 Diabetes

The GEMINI trial, (*G*lycemic *E*ffects in Diabetes *M*ellitus: Carved*I*lol-Metoprolol Comparis*o*N in Hypertens*I*ves), was a randomized, double-blind, parallel group, multi-center trial that compared the effects of carvedilol and metoprolol tartrate on glycemic control in patients with hypertension and type 2 diabetes. Patients receiving an angiotension converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) between the ages of 36 – 85 years with an HbA1c of 6.5% to 8.5% and BP >130/80 mmHg (but <180/110 mmHg) were randomized in a 2:3 ratio to receive carvedilol 6.25-25 mg BID (n = 498) or metoprolol tartrate 50-200mg BID (n = 737). Blood pressure medications were titrated every 1-2 weeks to target and then maintained for 5 months (if baseline SBP was 140-179mmHg then the target was <135mmHg, if baseline SBP is 130-140mmHg then target was <130mmHg, for DBP the target was <85mmHg if baseline was between 90-109mmHg or <80 if baseline DBP was between 80-90mmHg). Hydrochlorothiazide and then a calcium channel blocker were added if needed to reach target blood pressure if maximum doses of B-blockers were inadequate. The mean age was 60 years, 44% were female, 75% were white in this study. The mean total daily dose of carvedilol was 35mg and metoprolol was 256mg.

There was a mean increase in HbA1c with metoprolol of 0.15% (SD 0.04%, $p < 0.001$); carvedilol caused a mean increase of 0.02% (SD 0.04%, $p = 0.65$). The increase from baseline was not significant for carvedilol. The difference between the mean change in HbA1c from baseline is 0.13% (95% CI 0.2% to $p = 0.004$). Approximately two percent (2.2%) of metoprolol patients compared to 0.6% of carvedilol patients withdrew from the study due to worsening glycemic control. No significant difference was noted between carvedilol or metoprolol in terms of blood pressure reduction or safety profile. (GEMINI study, Bakris et al.)

Table 4: Change in blood pressure, heart rate and HbA1c with carvedilol or metoprolol in diabetic patients

Drug	Change in Blood Pressure (mmHg)	Change in Heart Rate (beats per minute)	Change in HbA1c
Carvedilol (6.25-25mg BID)	-18.1/-9.9	-6.1	+0.02%
Metoprolol (25-200mg BID)	-16.9/-9.5	-8.5	+0.15%

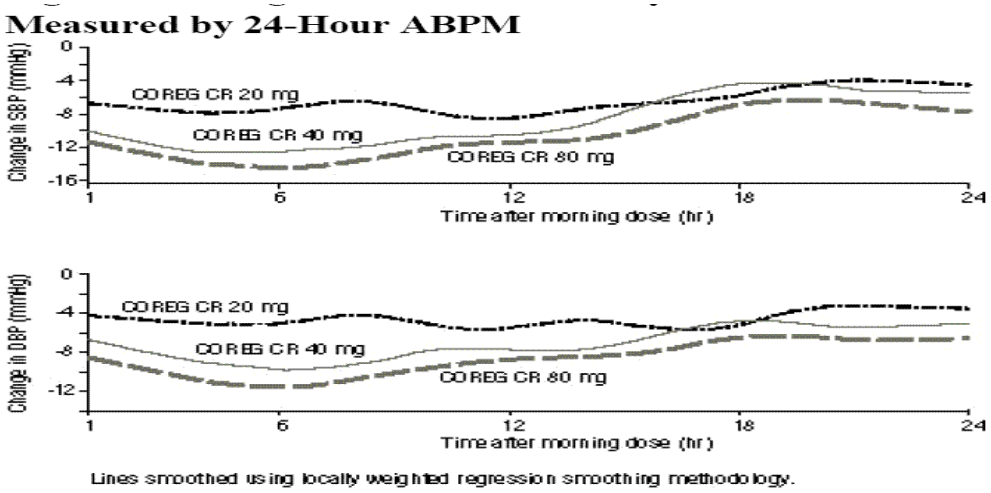
Carvedilol Controlled Release (Coreg CR®)

The efficacy of carvedilol controlled release has been evaluated in one multicenter, randomized, double-blind, placebo-controlled, parallel-group trial.[5,6,7] Three subsets of patients with essential hypertension were recruited for this trial (1) those with uncontrolled hypertension (sitting diastolic blood pressure (DBP) ≥90mmHg and ≤109mmHg) on no treatment, (2) those with a history of hypertension but controlled (DBP>90mmHg) on antihypertensive therapy, and (3) those with uncontrolled hypertension (DBP ≥90mmHg and ≤109mmHg) despite treatment with up to 2 antihypertensive agents not ß-blockers. Patients were randomized to placebo, carvedilol 20, 40 and 80mg daily and force-titrated every 2 weeks to target dose. Measurements were obtained using ambulatory blood pressure monitoring (ABPM). The mean age of the patients was 53 years old, 66% were male, 84% were on no antihypertensive medications at baseline and baseline systolic blood pressure (SBP) and DBP was 150/99mmHg.

The primary outcome of this trial was the change in mean 24-hour DBP as measured by ABPM. A statistical difference was found in DBP when all doses were compared to placebo (P≤0.001). Other results from this trial are listed in table #.

Table #5: Carvedilol controlled-release change in blood pressure and heart rate

Dose	Change in mean 24-hour SBP/DBP from baseline to week 6 (mmHg)	Change in mean SBP/DBP from baseline to mean peak (3-7 hours post dose) (mmHg)	Changes in mean SBP/DBP from baseline to mean trough (20-24 hours post dose) (mmHg)	Change in mean heart rate from baseline to week 6 (beats per minute)
Placebo (n=67)	-0.63/-0.36	0.00/+0.38	+0.09/+0.04	+0.1
20mg daily (n=76)	-6.75/-4.39	-7.13/-4.21	-3.22/-2.75	-6.6
40mg daily (n=66)	-10.06/-7.92	-13.69/-9.80	-4.77/-5.12	-7.3
80mg daily (n=75)	-12.48/-9.56	-15.29/-11.43	-8.35/-7.33	-9.9



Conclusions:

Clinical trial data support the use of three beta blockers in heart failure: carvedilol (Coreg), metoprolol succinate (Toprol XL), and bisoprolol (Zebeta). Like long-acting metoprolol, carvedilol appears to be equally efficacious in blacks and whites (Hanks, 2006). Compared to other beta-blockers, carvedilol may have less of an adverse effect on carbohydrate and lipid metabolism (Bakris GL, 2004).

Recommendation:

Carvedilol: recommended for addition to the formulary

Carvedilol extended-release: not recommended for addition to the formulary

References:

Bakris GL, Fonseca V, Katholi RE, et al. Metabolic effects of carvedilol versus metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA* 2004:292:2227-36.

The COMET Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET). *Lancet* 2003;362(9377):7-13.

Coreg® (carvedilol) package insert. Research Triangle Park, NC: GlaxoSmithKline; July 2008.

Data on file. Study SK&F 105517/095C1109, 1992. GlaxoSmithKline.

Data on file. Study SK&F 105517/028 (B104), 1992. GlaxoSmithKline.

Greenberg BH. A multi-center, randomized, double-blind, double-dummy, parallel-group study to compare effects of Coreg CR and Coreg IR on left ventricular end-systolic volume index in subjects with stable chronic heart failure (COMPARE). Heart Failure Society of America 2008 Scientific Meeting; September 22, 2008; Toronto, ON. Late-breaking clinical trials I (presented on Medscape Heartwire 2008).

Hanks, SD. Overview of Beta Blockers for Systolic Heart Failure. P&T 2006;31: 112-116.

Lacy CF, Armstrong LL, Goldman MP, Lance LL. Lexi-Comp. Drug Information Handbook. 17th edition, 2008-2009.

Packer M, Coats AJS, Fowler MB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) Study. *Circulation* 2002;106:2194-9.

Prepared by:

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Guanfacine (Tenex™)

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: 03-27-09

Name of practitioner submitting the application: Ann Richards, Pharm.D. (for 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)): San Antonio State Hospital

Information regarding new drug:

Therapeutic Classification	Andrenegic Agonist
Generic Name	Guanfacine
Trade Name(s)	Tenex ™
Manufacturer(s)	generic
Dosage Form(s)	

Explain the pharmacological action or use of this drug:
See Monograph

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

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

****

☐ application is approved

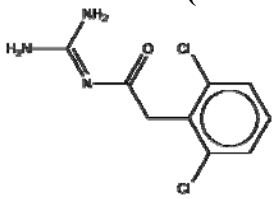
Ann L. Richards
signature of chairman of facility pharmacy and therapeutics committee

OR

☐ application is appropriate and complete

signature of clinical/medical director or designee

Guanfacine ER (Intuniv)



Classification: α_2 Adrenergic Agonist

Pharmacology: Guanfacine hydrochloride is a centrally acting antihypertensive which stimulates the α_2 adrenergic receptor thereby decreasing the output of the presynaptic norepinephrine neuron. The reduced sympathetic nerve impulses from the vasomotor center to the heart and blood vessels results in a slight reduction in heart rate (5 beats/minute) and peripheral vascular resistance.[1]

Other α_2 adrenergic agonists such as clonidine have shown beneficial effects as non-first line agents in children with Attention Deficit Hyperactivity Disorder (ADHD). Guanfacine, an agent similar to clonidine may be an alternative based on a longer half-life, decreased sedative and hypotensive properties, and more selective binding profile. It appears that α_2 adrenergic agonists may exert psychoactive effects via direct effects on the noradrenergic neurotransmitter system, indirectly affecting serotonin and dopamine transmission.[1,2] In addition, α_2 adrenergic agents may decrease tics in children with ADHD and tic disorders.[3]

Pharmacokinetics: [2,4]

Absorption: Referenced to an intravenous dose of 3 mg, the absolute oral bioavailability of guanfacine is about 80%. The time to peak plasma concentrations (Tmax) occur from 1 to 4 hours with an average of 2.6 hours after single oral doses or at steady state. The area under the concentration-time curve (AUC) increases linearly with the dose.

Distribution: The drug is approximately 70% bound to plasma proteins, independent of drug concentration. The whole body volume of distribution is high (a mean of 6.3 L/kg), which suggests a high distribution of drug to the tissues.

Metabolism: Metabolism occurs in the liver, primarily to the glucuronide and sulfate of 3-hydroxy guanfacine; oxidized mercapturic acid derivatives and other minor metabolites. It is unclear if metabolites have any pharmacologic activity.[5]

Elimination: Guanfacine and its metabolites are excreted primarily in the urine. In individuals with healthy renal function, the average elimination half-life is approximately 17 hours (range, 10 to 30 hours). Approximately 50% (40% to 75%) of the dose is eliminated in the urine as unchanged drug; the remainder is eliminated mostly as conjugates of metabolites produced by oxidative metabolism of the aromatic ring.

Indications:[2] Guanfacine is indicated for the treatment of hypertension either alone or in combination with other antihypertensives.

Off-label Uses: Attention deficit hyperactivity disorder (ADHD)
(Shire has received Complete Response Letter from FDA for Intuniv; marketing approval pending)

Tourette's Syndrome (children/adolescents)

Dosage and Administration:[1] The recommended initial dose of guanfacine hydrochloride when given in combination with another antihypertensive drug is 1 mg daily given at bedtime to minimize somnolence. If after 3 to 4 weeks of therapy, 1 mg does not give a satisfactory result, a dose of 2 mg may be given.

Off-label Dosing:[2]

ADHD: Initial doses of 0.5 mg/day with increases of 0.5 mg every 3 to 4 days or 0.25 to 0.5 mg every 5 to 7 days as needed or tolerated.

Tourette's Syndrome (children/adolescent): 0.5 mg orally once daily titrated slowly based on response and adverse reactions to a maximum dose of 4 mg/day in 3 divided doses.

Contraindications:[1,2] Hypersensitivity to guanfacine hydrochloride or any component of the formulation.

Precautions:[1]

- Sedation is usually dose related and most pronounced at initiation of therapy. Consider the potential for additive sedation when used centrally active depressants.
- Avoid abrupt withdrawal due to potential for rebound hypertension.
- Cerebrovascular disease
- Chronic liver disease
- Recent myocardial infarction
- Chronic renal failure
- Severe coronary insufficiency
- Pregnancy category B

Interactions:[1,2]

- Co-administration with other CNS-depressant drugs increases the potential for sedation
- The administration of guanfacine concomitantly with a CYP-450 enzyme inducer (phenobarbital or phenytoin) in patients with renal impairment resulted in significant reductions in elimination half-life and plasma concentration. More frequent dosing may be required to achieve or maintain the desired hypotensive response.
- Co-administration of tricyclic antidepressants may impair the antihypertensive effects of guanfacine
- Administration of bupropion and guanfacine may result in increased risk of seizure activity in the presence of no previous seizure history
- Co-administration with yohimbine may counteract the hypotensive effects of guanfacine due to opposing mechanisms of action

Adverse Reactions:[2]

- Similar to those of other central α_2-adrenoreceptor agonists: dry mouth, sedation (somnolence), weakness (asthenia), dizziness, constipation, and impotence
- Most are mild and tend to disappear on continued dosing

Comparison of Guanfacine and Clonidine Adverse Reactions

Adverse Reactions	Guanfacine (n=279)	Clonidine (n=278)
Dry mouth	30%	37%
Somnolence	21%	35%
Dizziness	11%	8%
Constipation	10%	5%
Fatigue	9%	8%
Headache	4%	4%
Insomnia	4%	3%

Cost Comparison of Attention Deficit Hyperactivity Disorder Agents

Generic Name	Brand Name	Average Daily Dose	AWP Cost (per tablet)	Net Cost (per tablet)
Amphetamine mixture	Adderall/ Adderall XR	40 mg	20mg – $0.54 20mgXR - $6.81	20mg - $0.22 20mg XR- $5.28
Dextroamphetamine	Dexedrine	40 mg	10mg - $2.02	10mg - $1.55
Methylphenidate immediate-release	Ritalin, Methylin, Metadate	60 mg	20mg - $0.69	20mg - $0.13
Methylphenidate sustained-release	Ritalin SR, Concerta, Metadate CD	60 mg	SR20mg - $1.19 54mg - $5.36 40mg - $5.61	SR20mg - $0.24 54mg - $3.96 40mg - $4.31
Methylphenidate long-acting	Ritalin LA	50/50 cmpd	30mg - $4.19 40mg - $4.31	30mg - $3.25 40mg - $3.34
Dexmethlyphenidate	Focalin / Focalin XR	20 mg	10mg - $1.62 XR 20mg - $4.85	10mg - $1.26 XR 20mg - $3.76
Lisdexamphetamine	Vyvanse	50 mg	$4.98	$3.79
Methylphenidate Transdermal system	Daytrana	30 mg	$5.75	$4.46
Atomoxetine	Strattera	80 mg	$6.22	$4.82
Clonidine*	Catapres	0.3 mg	$0.47	$0.11
Bupropion*	Wellbutrin SR	300 mg	150mg - $2.91	150mg - $0.41
Guanfacine*	Texex	2 mg	$1.18	$0.51

* Not FDA approved for the treatment of ADHD
- Shaded rows indicate non-formulary items

Therapeutic Monitoring:[1]

Hypertension: blood pressure to meet individualized patient goals

ADHD: Improvement is mental and behavioral symptoms (inappropriate attention, impulsivity, hyperactivity, and cognitive performance). Use of a validated ADHD rating scale to guide therapy is recommended.[6]

Toxicity Monitoring:

-Liver enzymes

-Evidence of cardiac disease

Product Identification:[2] **(**available as generic)

Tenex™	1mg tablets light pink diamond shaped
Tenex™	2 mg tablets yellow diamond shaped

Efficacy:

1) Guanfacine demonstrated beneficial affects in both parent and clinician ratings of symptoms and behavior during preliminary trials in 13 patients with DSM-III-R criteria for attention deficit hyperactivity disorder (ADHD). Behavioral scores were assessed at baseline and again after approximately 1 month of therapy. It was unknown whether patients were off all other ADHD medications prior to initial assessment. Doses of guanfacine were titrated to optimal effect. Initial dose was 0.5 mg daily, with increments of 0.5 mg every third day. The mean dose was 3.2 mg daily with a maximum of 4 mg. Dosing was divided into 4 uneven doses, with lower equal doses in the morning, noon, and 1600 hours, and the largest dose at bedtime. Parent assessment of subsets of the Conners 31-item Questionnaire, showed improvement in 3 factors (hyperactivity, inattention, and immaturity), with no change in mood or aggression/opposition. No changes in blood pressure were noted. Initial sedation and tiredness resolved within 2 weeks. Decreased appetite was noted in 16%.[7]

2) A small randomized, double-blind trial found an 8-week course of guanfacine to be safe and effective in children with attention deficit hyperactivity disorder (ADHD) and comorbid mild-to-moderate TIC Disorders (n=34; mean age 10.4 years, range 7 to 14 years). Entry criteria included a diagnosis of any type of ADHD and any type of tic disorder (both diagnoses based on DSM-IV criteria), as well as a Conners hyperactivity index score greater than or equal to 1.5 standard deviation units for age and gender. Guanfacine dosing began with 0.5 mg at bedtime for 3 days, followed by 0.5 mg in the morning and at bedtime for 4 days, and then 0.5 mg in the morning, afternoon, and evening (dose could be adjusted upward by the primary physician, maximum 4 mg/day). After 8 weeks, the teacher-rated ADHD Rating Scale showed significant improvement among guanfacine-treated children for inattention score ($p=0.005$) and hyperactive/impulsive score ($p=0.006$). Total scores dropped by 37% and 8% in the guanfacine and placebo groups, respectively ($p< 0.001$). Investigator ratings on the Clinical Global Impression (CGI) scale indicated 9 of 17 guanfacine-treated subjects were much or very much improved, compared to none in the control group ($p< 0.001$). Scores on the Yale Global Tic Severity Scale decreased by 31% and 0% for the guanfacine and control groups, respectively ($p=0.05$). With respect to the Continuous Performance Test, the guanfacine group exhibited 22% and 17% reductions in commission and omission errors, respectively, while the placebo group had 29% and 31% increases in the same 2 types of errors (commission, $p=0.01$; omission, $p=0.04$). Mild sedation was reported by 6 in the guanfacine group; 1 subject withdrew due to sedation. Other side effects of guanfacine included mid-sleep awakening (n=3), dry mouth (n=4), constipation (n=2), and morning loss of appetite (n=2); no serious side effects were associated with guanfacine therapy.[8]

3) In a preliminary study guanfacine improved symptoms of attention-deficit hyperactivity disorder (ADHD) in children with comorbid TIC disorders. Ratings of tic severity and ADHD symptoms in the 10 children, aged 8 to 16 years, were made on four scales; most subjects were treated at 1.5 mg/day and followed up between 4 and 20 weeks. Both commission and omission errors declined significantly and the severity of motor and phonic tics decreased significantly.

Lethargy or fatigue were common but transient. However, individuals varied in the magnitude and direction of treatment response.[9]

Safety:
In open trials, most patients experienced adverse reactions including fatigue, headache, insomnia, sedation, or irritability. Patient withdrawals were due to headaches, sedation, and over arousal. Insignificant decreases in blood pressure and pulse were noted in an 8-week trial. To minimize changes in blood pressure monitor during the dosage adjustment phase of treatment and taper slowly to prevent rebound hypertension upon discontinuation.

In several case reports, the combination of guanfacine for ADHD with concurrent neuroleptics or antidepressants (eg, venlafaxine, bupropion) has resulted in significant side effects, including severe dystonia, mania, and in 1 case, seizures.[10,11] However little is known about the interactive potential of guanfacine and these drugs. In two patients previously stabilized on valproic acid therapy with therapeutic concentrations, the addition of guanfacine resulted in increased plasma valproate concentrations requiring dosage reductions.[12]

Conclusions:
Guanfacine offers advantages over other centrally-acting α_2 adrenergic agonist such as clonidine. Its longer elimination half-life, enables once-daily administration and may contribute to the less-severe withdrawal reactions. Guanfacine may also cause fewer side effects than clonidine (dry mouth, sedation).[1] For parents who are resistant to placing their children on stimulant agents or in children unable to tolerate clondine, guanfacine is another fairly inexpensive alternative.

Recommendation: Addition to the formulary

References:

1. Micromedex Healthcare Series Web site. http://www.thomsonhc.com. Via HHSC intranet. Accessed Mar 15, 2009.

2. Facts & Comparisons. Facts & Comparisons Web site. http://online.factsandcomparisons. Via HHSC intranet. Accessed March 15, 2009.

3. Newcorn JH, et al. Alpha adrenergic agonists. Neurochemistry, efficacy and clinical guidelines in children. *Ped Clin N Amer*. 1998;45:1099-1122.

4. Tenex package insert. A H Robins, revised received 6/92., 11/89.

5. Kiechel JR: Pharmacokinetics and metabolism of guanfacine in man: a review. *Br J Clin Pharmacol.* 1980b; 10(suppl 1):25S-32S.

6. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder. *J. Am. Acad. Child Adolesc. Psychiatry.* 2007;46(7):894-921.

7. Hunt RD, Arnsten AFT, & Asbell MD: An open trial of guanfacine in the treatment of attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 1995; 34(1):50-54.

8. Scahill L, Chappell PB, Kim YS, et al: A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. *Am J Psychiatry*. 2001; 158:1067-1074.

9. Chappell P, Riddle M, Scahill L, et al: Guanfacine treatment of comorbid attention-deficit hyperactivity disorder and Tourette's syndrome: preliminary clinical experience. *J Am Acad Child Adolesc Psychiatry*. 1995; 34(9):1140-1146.

10. Chong Y, et al. Dystonia as a side effect of neuroleptics. *J Am Acad Child Adolesc Psychiatry*. 1999;38:793-795.

11. Tilton P. Bupropion and guanfacine. *J Am Acad Child Adolesc Psychiatry*. 1998;37:682.

12. Ambrosini P, Sheikh RM. Increased plasma valproate concentrations when coadministered with guanfacine. *J Child Adolesc Psychopharmacol*. 1998;8:143-147

Linezolid (Zyvox)

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: 03-27-09

Name of practitioner submitting the application: Ann Richards, Pharm.D.

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)): San Antonio State Hospital

Information regarding new drug:

Therapeutic Classification	Antibiotic, Oxazolidinone
Generic Name	Linezolid
Trade Name(s)	Zyvox®
Manufacturer(s)	
Dosage Form(s)	

Explain the pharmacological action or use of this drug:
See monograph

Explain the advantages of this drug over those listed in the formulary:
Is used as a third-line regimen for MDR-TB and XDR-TB

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

****

☐ application is approved

Ann L. Richards
signature of chairman of facility pharmacy and therapeutics committee

OR

☐ application is appropriate and complete

signature of clinical/medical director or designee

Linezolid
(Zyvox ®)

Classification : Antibiotic, Oxazolidinone

Pharmacology:

Linezolid is a synthetic antibacterial agent. It inhibits bacterial protein synthesis by binding to bacterial 23S ribosomal RNA of the 50S subunit. This prevents the formation of a functional 70S initiation complex that is essential for the bacterial translation process. Linezolid is bacteriostatic against enterococci and staphylococci and bactericidal against most strains of streptococci.

Pharmacokinetics:

Absorption: Rapidly and extensively absorbed after oral dosing. Maximum plasma concentrations are reached approximately 1 to 2 hours after dosing, and the absolute bioavailability is approximately 100%. Therefore, linezolid may be given orally or intravenously without dose adjustment.

Distribution: Linezolid readily distributes to well-perfused tissues. The plasma protein binding of linezolid is approximately 31% and is concentration-independent. The volume of distribution of linezolid at steady-state averaged 40 to 50 liters in healthy adult volunteers.

Metabolism: Hepatic via oxidation of the morpholine ring, resulting in two inactive metabolites (aminoethoxyacetic acid, hydroxyethyl glycine); does not involve CYP.

Bioavailability: 100%

Elimination: Half-life elimination in adults 4-5 hours. Time to peak in adults, oral is 1-2 hours.

Indications:

Vancomycin-Resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia. Nosocomial pneumonia, complicated skin and skin structure infections, community acquired pneumonia including concurrent bacteremia.

Non-FDA approved indication: Treatment of mycobacterial infections. Linezolid has been used as a third-line regimen for the treatment of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB).

Dosage and Administration:

Dosage Guidelines for Linezolid

Infection	**Dosage and Route of Administration Adults and Adolescents (12 Years and Older)**	**Recommended Duration of Treatment (consecutive days)**
Complicated skin and skin structure infections	600 mg IV or oral q 12h	10 to 14
Community-acquired pneumonia, including concurrent bacteremia		
Nosocomial pneumonia		
Vancomycin-resistant *Enterococcus faecium* infections, including concurrent bacteremia	600 mg IV or oral q 12h	14 to 28
Uncomplicated skin and skin structure infections	Adults: 400mg oral q12h Adolescents: 600mg oral q12h	10 to 14
Tuberculosis (MDR-TB or XDR-TB)	600 mg IV or oral daily	Up to 2 yrs until sputum culture conversion if tolerated

Take with or without food. Avoid tyramine-containing foods/beverages.

Contraindications:

Linezolid formulations are contraindicated for use in patients who have known hypersensitivity to linezolid or any of the other product components.

Warnings/Precautions:

Myelosuppression has been reported and may be dependent on duration of therapy (generally >2 weeks of treatment); use with caution in patients with pre-existing myelosuppression, in patients receiving other drugs which may cause bone marrow suppression, or in chronic infection (previous or concurrent antibiotic therapy). Weekly CBC monitoring is recommended. Discontinue linezolid in patients developing myelosuppression (or in whom myelosuppression worsens during treatment).

Lactic acidosis had been reported with use. Linezolid exhibits mild MAO inhibitor properties and has the potential to have the same interactions as other MAO inhibitors; use with caution in uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or untreated hyperthyroidism; avoid use with serotonergic agents such as TCAs, venlafaxine, trazodone, sibutrimine, meperidine, destromethorphan, and SSRIs; concomitant use has been associated with the development of serotonin syndrome. Unnecessary use may lead to the development of resistance to linezolid; consider

alternatives before initiating outpatient treatment.

Peripheral and optic neuropathy has been reported in patients treated with linezolid, primarily those patients treated for longer than the maximum recommended duration of 28 days. Visual function should be monitored in all patients taking linezolid for extended periods (=> 3 months) and in all patients reporting new visual symptoms regardless of length of therapy with linezolid.

Seizures have been reported; use with caution in patients with a history of seizures. Prolonged use may result in fungal or bacterial superinfection, including *C. difficile* associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months after antibiotic treatment.

Interactions:

Linezolid is a reversible, nonselective inhibitor of MAO. Serotenergic agents (e.g., TCA's, venlafaxine, trazodone, sibutramine, meperidine, dextromethorphan, and SSRIs) may cause a serotonin syndrome (eg, agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, tachycardia, hyperpyrexia, cognitive dysfunction) when used concomitantly. Adrenergic agents (eg, phenylpropanolamine, pseudoephedrine, sympathomimetic agents, vasopressor or dopaminergic agents) may cause hypertension. Tramadol may increase the risk of seizures when used concurrently with linezolid. Myelosuppressive medications may increase risk of myelosuppression when used concurrently with linezolid.

Adverse Reactions:

The most common adverse events in patients treated with linezolid were diarrhea (incidence across studies: 2.8% to 11.0%), headache (incidence across studies: 0.5% to 11.3%), and nausea (incidence across studies: 3.4% to 9.6%).

Other adverse events reported in Phase 2 and Phase 3 studies included oral moniliasis, vaginal moniliasis, hypertension, dyspepsia, localized abdominal pain, pruritis, and tongue discoloration.

Cost:

Generic Name	**Brand Name**	**Strength**	**AWP Cost (per tablet)**	**Net Cost (per tablet)**
Linezolid	Zyvox®	600 mg	67.39	67.38
Linezolid	Zyvox®	600 mg	UD-91.24	UD-67.38
Generic Name	**Brand Name**	**Strength**	**AWP Cost (Infusion-Premixed)**	**Net Cost (Infusion-Premixed)**
Linezolid	Zyvox®	600 mg	119.15	86.35
Generic Name	**Brand Name**	**Strength**	**AWP Cost (Powder for OS)**	**Net Cost (Powder for OS)**
Linezolid	Zyvox®	20mg/ml-150 ml	456.23	336.23

Monitoring:

Weekly CBC and platelet counts, particularly in patients at increased risk of bleeding, with pre-existing myelosuppression, on concomitant medications that cause bone marrow suppression, in those that require >2 weeks of therapy, or in those with chronic infection who have received previous or concomitant antibiotic therapy; visual function with extended therapy (=>3 months) or in patients with new onset visual symptoms, regardless of therapy length.

Product Identification:

Tablets

White, capsule shaped, film coated 600 mg

Powder for Oral Suspension

Orange Flavor, 100mg/5ml

Injection

Ready to use bag, 100,200 and 300ml single-use, 2mg/ml

Efficacy:

Linezolid formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms: Vancomycin-resistant *Enterococcus faecium* (VRE) infections, including cases with concurrent bacteremia; nosocomial pneumonia causes by *Staphylococcus aureus* (methicillin-susceptible and –resistant strains) or *Streptococcus pneumoniae* (including multi-drug resistant strains, which refer to isolates resistant to 2 or more of the following antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole); community-acquired pneumonia caused by *S. pneumoniae* (including multi-drug resistant strains), including cases with concurrent bacteremia, or *S. aureus* (methicillin-susceptible strains only); complicated skin and skin structure infections, including diabetic foot infections, without concomitatnt osteomyelitis, caused by S. Aureus (methicillin-susceptible and-resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*; and uncomplicated skin and skin structure infections caused by *S. Aureus* (methicillin-susceptible strains only) or *S. pyogenes*.

Linezolid has significant in vitro acitivity against *M. tuberculosis*, and has occasionally been used to treat TB. There have been a few anecdotal reports of linezolid for the treatment of MDR-TB and XDR-TB.

Conclusion:

Linezolid it the first oral antibiotic to be approved from the oxazolidinone class with demonstrated *in vitro* activity against both drug-susceptible and drug-resistant isolates of *Mycobacterium tuberculosis* without cross-resistance with the standard antituberculous agents.

Recommendation:

Add to formulary reserve class drug for Texas Center for Infectious Disease for MDR-TB and XDR-TB. Linezolid is a third-line regimen for the treatment of XDR-TB according to drug sensitivities where no acceptable alternative exists among the available drugs. Add to formulary reserve class for FDA indications when prescribed by Infectious Disease Specialist.

References:

1. Zyvox® (linezolid) [package insert]. New York, NY: Pfizer Inc., America; July 2006.
2. Lacy C, Armstrong L, Goldman M, Lance L, Linezolid, Drug Information Handbook Lexi-Comp Inc., 17th Edition, 2008-2009, 927-929.
3. Brown-Elliott et al.,Abstr. Annu. Meet.Infect. 2002
4. Alla A, [Letter], Pfizer U.S. Medical Information, March 2009.
5. Condos R, Hadgiangelis N, Leibert E, Jacquette G, Harkin T, Rom W. Case Series Report of a Linezolid-Containing Regimen for Extensively Drug-Resistant Tuberculosis. Chest 2008;134;187-192.
6. Alcala, L, Ruiz-Serrano, MJ, Perez-Fernandez Turegano, C, et al. In vitro acitivities of linezolid against clinical isolates of Mycobacterium tuberculosis that are susceptible or resistant to first-line antituberculosis drugs. Antimicrob Agents Chemother 2003; 47:416
7. Ntziora,F, Falagas,ME. Linezolid for the treatment of patients with [corrected] Mycobacterial infections[corrected] a systematic review. Int J Tuberc Lung Dis 2007; 11:606

Prepared by:

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March 2009

Classes of Medications Frequently Used for Psychiatric Indications

Consent is required for any medication that is used in the treatment of a psychiatric diagnosis or symptom, whether or not the medication is included in this list. Refer to physician order for determination of indication for use.

The classification of psychotropic medication is fairly standard but medications can be used for treatment of illnesses that would be considered listed under a different classification. For example, some medications listed under antipsychotics maybe used as a mood stabilizer.

The Executive Formulary Committee does not endorse the use of nonformulary drugs

Antidepressants

amitriptyline (Elavil)
amoxapine (Asendin)
bupropion (Wellbutrin, Wellbutrin SR)
bupropion (Wellbutrin XL) *nonformulary*
citalopram (Celexa)
desipramine (Norpramin)
desvenlafaxine (Pristiq) *nonformulary*
doxepin (Sinequan)
duloxetine (Cymbalta)
escitalopram (Lexapro)
fluoxetine (Prozac)
imipramine (Tofranil)
maprotiline (Ludiomil)
mirtazapine (Remeron, Remeron SolTab)
nefazodone (Serzone) *nonformulary*
nortriptyline (Pamelor, Aventyl)
paroxetine (Paxil, Paxil CR)
protriptyline (Vivactil)
sertraline (Zoloft)
trazodone (Desyrel)
trimipramine (Surmontil)
venlafaxine (Effexor, Effexor XR)

Antipsychotics

aripiprazole (Abilify)
chlorpromazine (Thorazine)
clozapine (Clozaril, Fazaclo)
droperidol (Inapsine) *nonformulary*
fluphenazine (Prolixin)
fluphenazine decanoate (Prolixin D)
haloperidol (Haldol)
haloperidol decanoate (Haldol D)
loxapine (Loxitane)
molindone (Moban)
olanzapine (Zyprexa, Zyprexa Zydis)
paliperidone (Invega)
perphenazine (Trilafon)
pimozide (Orap) *nonformulary*
quetiapine (Seroquel)
risperidone (Risperdal, Risperdal M-Tab)
risperidone (Risperdal Consta)
thioridazine (Mellaril)

Anxiolytics/Sedatives/Hypnotics

alprazolam (Xanax, Xanax XR)
amobarbital (Amytal)
buspirone (BuSpar)
chloral hydrate (Noctec)
chlordiazepoxide (Librium)
clonazepam (Klonopin)
clorazepate (Tranxene)
diazepam (Valium)
diphenhydramine (Benadryl)
eszopiclone (Lunesta) *nonformulary*
flurazepam (Dalmane) *nonformulary*
hydroxyzine (Atarax, Vistaril)
lorazepam (Ativan)
oxazepam (Serax)
pentobarbital (Nembutal) *nonformulary*
ramelteon (Rozerem) *nonformulary*
temazepam (Restoril)
triazolam (Halcion)
zolpidem (Ambien)
zaleplon (Sonata)

Mood Stabilizers

carbamazepine (Tegretol, Tegretol XR, Carbatrol, Equetro)
divalproex sodium (Depakote, Depakote ER)
lithium (Eskalith, Eskalith CR, Lithobid)
valproic acid (Depakene)
oxcarbazepine (Trileptal)
lamotrigine (Lamictal)
topiramate (Topamax)

Stimulants

amphetamine/dextroamphetamine mixture (Adderall, Adderall XR)
dexmethylphenidate (Focalin) *nonformulary*
dextroamphetamine (Dexedrine)
lisdexamfetamine (Vyvanse) *nonformulary*
methamphetamine (Desoxyn) *nonformulary*
methylphenidate (Ritalin, Ritalin SR, Concerta, Metadate, Metadate CD)
methylphenidate patch (Daytrana) *nonformulary*

Miscellaneous Drugs

thiothixene (Navane)
trifluoperazine (Stelazine)
ziprasidone (Geodon)

Monoamine Oxidase Inhibitors

phenelzine (Nardil)
tranylcypromine (Parnate)
isocarboxazid (Marplan)
selegiline (Emsam) *nonformulary*

Other

This category must be approved prior to inclusion in this instrument

Update 03-27-09

atomoxetine (Strattera)
atenolol (Tenormin)
clomipramine (Anafranil)
clonidine (Catapres)
fluvoxamine (Luvox)
gabapentin (Neurontin)
guanfacine (Tenex)
metoprolol (Lopressor)
nadolol (Corgard)
propranolol (Inderal)

Miscellaneous Drugs (continued)

reserpine (Serpasil) *nonformulary*
naltrexone (ReVia)
olanzapine/fluoxetine (Symbyax) *nonformulary*
pindolol (Visken) *nonformulary*