

DADS/DSHS EXECUTIVE FORMULARY COMMITTEE MINUTES
August 22, 2008

The Executive Formulary Committee convened on Friday, August 22, 2008 in Conference Room 240 - CO Building 2. The meeting was called to order by Dr. Matthews, Chair at 9:35 a.m.

Janet Adams, MSN, RN, CNS	Absent	Kenny Dudley (non-voting)	Absent
Emilie A. Becker, M.D.	√	Denice Geredine (non-voting)	Absent
Rosha Chadwick, R.Ph.	Absent	Mike Maples (non-voting)	Absent
Jeanna Heidel, Pharm.D.	√	Bob Burnett (non-voting)	Absent
J. Brett Hood, M.D.	√	Jay Norwood, MSN, RN (non-voting)	Absent
Jeff Matthews, M.D.	√	Julie McRae, MS, RN, CDDN (non-voting)	Absent
Lisa Mican, Pharm.D.	√	Vacant Medical Director	
Connie Millhollon, RN,	√	Vacant Center Position	
Ann L. Richards, Pharm.D.	√	Vacant Center Position	
Bill Race, M.D.	Absent	Vacant Center Position	
Lilani Muthali, M.D. (non-voting)	√	Vacant Center Position	
Nina Jo Muse, M.D. (non-voting)	Absent	Vacant State School Position	

Guest Present: Laura West, Pharm.D. Student Volunteer, Austin State Hospital

Approval of Minutes of May 16, 2008

On a motion of Dr. Becker, seconded by Dr. Heidel, the minutes of the May 16th meeting were approved as previously distributed.

Adverse Drug Reaction Reports

The Executive Formulary Committee received three adverse drug reaction reports. A 16 year old male was admitted on 6/23/08 to a State Hospital. He was taking divalproex (Depakote®) ER 1,000 mg daily, risperidone (Risperdal®) 3 mg at bedtime and methylphenidate (Concerta®) 27 mg every morning. On admission, the patient's CBC showed WBC 3.7 K/mm³, ANC 1.4 K/mm³ and platelets 233 K/mm³. The valproic acid plasma level was 55.9 mcg/ml. The divalproex was increased to 2,000 mg at bedtime due to mood lability. The methylphenidate was held at admission and not restarted. Follow up labwork obtained on June 30th showed WBC 3.3 K/mm³, ANC 0.7 K/mm³, platelets 224 K/mm³ and a valproic acid level of 121.1 mcg/ml. Divalproex was discontinued on July 1st secondary to neutropenia and leukopenia. Lithium was initiated for mood stabilization and to promote leukocytosis. Follow up CBC on July 5th showed a WBC 3.1 K/mm³ and ANC 1.3 K/mm³.

In the second case, an 11 year old female was admitted in early May on divalproex (Depakote®) ER 1,250 mg at bedtime and quetiapine 150 mg in the morning and 500 mg at bedtime with a WBC of 3.5 K/mm³ and ANC of 1.0 K/mm³. The divalproex dose was decreased to 1,000 mg at bedtime and the quetiapine dose was decreased to 150 mg in the morning and 350 mg at bedtime. On May 16th, the WBC was 3.1 K/mm³ and the ANC was 0.8 K/mm³. The divalproex dose was reduced and subsequently discontinued. On May 19th, the WBC was 4.0 K/mm³ and ANC of 1.0 K/mm³. The quetiapine dose was reduced and eventually discontinued. The WBC eventually rebounded to 4.1 K/mm³ and ANC 1.7 K/mm³ on June 17th.

In discussing the previous adverse drug reaction of divalproex with quetiapine, Dr. Mican noted that at Austin State Hospital there was a clinical impression that the combination of divalproex with quetiapine in the child/adolescent population caused more reduction in WBC and ANC. Consequently, a retrospective review of cases was completed in the child/adolescent population at Austin State Hospital. For this review, a retrospective evaluation of discharged patients from the child and adolescent psychiatric services was completed. A total of 133 patients were included in the evaluation. Fifty patients were in the monotherapy valproate group, 33 patients in the monotherapy quetiapine group and 50 patients in the combination of quetiapine and valproate group. Patients had to be on these drugs for at least 4 days and had to have at least one follow up WBC and ANC. Patients in the valproate group had to achieve a serum level of at least 50 mcg/ml to be included in the study. The incidence rates of neutropenia for the combination of valproate and quetiapine in this population was 44%. For the monotherapy valproate group the incidence rate was 26% and for the quetiapine group it was 6%. According to Dr. Mican, this resident research project will be submitted for publication. The Committee recommended that information about this potential adverse effect of the combination of divalproex and quetiapine in the child/adolescent population be distributed to the field.

The last adverse drug reaction report reviewed occurred in an employee that received an influenza vaccine. On the day that the employee received the injection, the employee noticed burning and itching around the injection site. It became worse spreading to arms, face, stomach, legs and back. The individual sought treatment from their personal physician eight days after vaccination and received treatment with oral corticosteroids and diphenhydramine and the rash resolved.

New Drug Applications

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

lisdexamfetamine (Vyvanse®) - discussed by Dr. Mican

Lisdexamfetamine is a pro-drug of dextroamphetamine. After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and converted to dextroamphetamine, which is responsible for the drug's activity. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine *in vitro*. Lisdexamfetamine is indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children aged 6 to 12 years, and adults over the age of 18. Lisdexamfetamine does not have an indication for the treatment of ADHD in 13 to 18 year olds. In looking at cost issues, lisdexamfetamine has a constant cost of \$3.54 for any capsule strength. Mixed amphetamine salts (Adderall®) XR is \$4 for any capsule strength. The immediate release mixed amphetamine salts tablet costs about \$0.22 each. Interesting to note that Vyvanse® and Adderall® XR are both manufactured by Shire and that Adderall® XR is scheduled to lose its patent protection in 2009. A recent publication by a poison control center raises safety concerns. This publication reports an unexpectedly frequent number of adverse drug reactions secondary to lisdexamfetamine. The records of 5 poison centers covering 8 states were reviewed for all human cases involving the product for the first 10 months postmarketing. Adverse reactions occurred on initial use of lisdexamfetamine in 22 of 28 (79%) reported cases. A total of 24 adverse drug reaction cases (86%) were reported within the first week after initiation of therapy. Approximately half of the patients had previously used stimulant therapy before. A majority of cases (89%) involved the drug lisdexamfetamine alone without other concomitant medications. The rate of reported ADRs with lisdexamfetamine during the first 10 months was more than 10 times the mean rate previously reported for amphetamines. Out of the patients examined by a health care provider,

clinical effects experienced in over 20% of patients included hallucinations (20%), insomnia (20%), dystonia (47%), agitation (53%), and tachycardia (73%). Lisdexamfetamine has comparable efficacy and safety to mixed amphetamine salts extended release (MAS-XR), however a recent postmarketing report noting a high frequency of adverse drug reactions with the product by the poison control center is concerning. The new indication of lisdexamfetamine for adult ADHD does not provide an added benefit over MAS or MAS-XR, which may also be used in this patient population. The studies reported included only previous responders to treatment and those without comorbid psychiatric illness, which is not representative of the institutions' patient populations. Currently, there is limited evidence regarding decreased abuse potential with this product. There is no clinical information to show that there is additional benefit of lisdexamfetamine regarding abuse potential over other currently available long acting stimulants. No short-acting version of lisdexamfetamine is currently available.

Following discussion, on motion of Dr. Becker, seconded by Dr. Hood, the request to add lisdexamfetamine (Vyvanse®) to the formulary was denied.

dexmethylphenidate extended release (Focalin XR®) - discussed by Dr. Mican

Dexmethylphenidate is the pharmacologically active *d*-threo enantiomer of racemic methylphenidate (Ritalin®). Dexmethylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Dexmethylphenidate is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in patients ages 6 years and older. The dose of dexmethylphenidate XR is 5 mg daily for pediatric patients and 10 mg daily for adult patients. The cost of dexmethylphenidate XR ranges from \$3.31 to \$3.45 per capsule. The price of dexmethylphenidate immediate release ranges from \$0.73 to \$1.05 per tablet for twice a day dosing. Concerta® pricing ranges from \$3.25 to \$3.74 per tablet and Metadate CD® ranges from \$2.87 to \$3.94 per capsule. Two safety and efficacy comparisons between dexmethylphenidate XR and methylphenidate products have been conducted. However, the comparison products in these studies were not kinetically similar. Dexmethylphenidate XR has 50% immediate-release and 50% delayed-release beaded formulation and the comparative product (Concerta®) is 22% immediate-release and 78% extended-release through an osmotic release system. Therefore, the studies completed showed the expected results based on the pharmacokinetics of each product. A better comparison would have been the Focalin XR® product to the Ritalin LA® product. Adequate studies are not available to conclude that Focalin XR® provides a superior drug profile in regard to safety, tolerability and efficacy with methylphenidate. Two studies comparing Focalin XR® to Concerta® found greater improvement with Focalin XR® in the earlier hours after dosing, whereas the effect of Concerta® lasted longer throughout the day and was superior in the later hours. The difference in time profile of effect between these agents is likely attributed to the different drug-release technologies and the percent of immediate-release versus extended-release composition of these products rather than the difference between dexmethylphenidate and methylphenidate. Side effects are similar between dexmethylphenidate and methylphenidate.

Following discussion, on motion of Dr. Hood, seconded by Dr. Becker, the request to add dexmethylphenidate extended release (Focalin XR®) to the formulary was denied.

Melatonin for the Supplement Section - discussed by Dr. Mican

At a previous meeting, a Supplement Section was added to the Drug Formulary. In order to qualify for addition to this section, a product has to have literature support and be USP verified. Melatonin is frequently listed on the non-formulary drug list. Therefore, the Committee recommended that it be reviewed for addition to the Drug Formulary in the Supplement Section. In reviewing the USP database, there was no USP verified product for melatonin; therefore melatonin is not eligible for addition to the Drug Formulary.

Psychotropic Audit Criteria – Comparison to TIMA

Dr. Muse requested that the Committee consider comparing the TIMA Guidelines to the monitoring parameters for consistency between the two documents. The Schizophrenia Clinician's Manual states the following:

“Routine health monitoring is essential to detection and management of side effects that may result from treatment with antipsychotic medications. As the use of atypical antipsychotic medications has become increasingly more widespread, several health implications have been recognized through case reports, post-marketing surveillance, and pharmacoepidemiological studies. Some antipsychotic medications have been associated with weight gain, dyslipidemia, hyperglycemia, and altered EKG findings. In addition, significant research suggests that patients with schizophrenia may be more likely to experience certain health conditions, such as diabetes, even in the absence of medication-related risk factors. Based on this information, the Texas public health system has adopted the Mount Sinai Conference health monitoring guidelines. These guidelines include recommendations for monitoring the physical health of patients receiving antipsychotic medications, including recommendation for the routine monitoring of metabolic side effects such as weight gain, diabetes, and hyperlipidemia. The Mt. Sinai Conference monitoring guidelines can be accessed using the following citation:

Marder SR, Essock SM, Miller AL, et al. Physical Health Monitoring of Patients With Schizophrenia. *American Journal of Psychiatry* 2004;161:1334-49.”

The current audit guidelines had originally incorporated the Mt. Sinai Conference Guidelines (the Marder reference) into the guidelines. In these guidelines for patients on second generation antipsychotics, the tardive dyskinesia evaluation is obtained every 12 months, except for high risk patients (including elderly) where the evaluation is obtained every 6 months. For first generation antipsychotics, it is recommended that the tardive dyskinesia evaluation be completed every six months except for high risk patients where it is recommended that the evaluation be completed every three months. However, the Texas Administrative Codes (TAC) required quarterly evaluation for movement disorders (tardive dyskinesia). On a motion of Dr. Becker, seconded by Dr. Mican, it was recommended that the Committee pursue the changing of the TAC to reflect the current standard of practice. Dr. Richards will follow up on this issue.

FDA Alerts

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

For conventional and atypical antipsychotics, the FDA notified healthcare professionals that both are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis. In April 2005, the FDA notified healthcare professionals that patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death. Since issuing that notification, the FDA has reviewed additional information that indicates the risk is also associated with conventional antipsychotics. Antipsychotics are not indicated for the treatment of dementia-related psychosis. The prescribing information for all antipsychotic drugs will now include that same information about this risk in a Boxed Warning and the Warnings section.

The FDA notified healthcare professionals of the risk of muscle injury, rhabdomyolysis, which can lead to kidney failure or death, when simvastatin (Zocor®) is used with amiodarone (Cordarone®). This risk is dose-related and increases when a dose of simvastatin greater than 20 mg per day is given with amiodarone. Although a revision of the simvastatin labeling in 2002 described an increased risk of rhabdomyolysis when amiodarone is taken with simvastatin doses greater than 20 mg daily, the FDA continues to receive reports of rhabdomyolysis in patients treated concurrently with amiodarone and simvastatin. Prescribers should be aware of the increased risk of rhabdomyolysis when simvastatin is prescribed with amiodarone, and they should avoid doses of simvastatin greater than 20 mg per day in patients taking amiodarone.

The FDA notified healthcare professionals that a Boxed Warning and Medication Guide are to be added to the prescribing information to strengthen existing warnings about the increased risk of developing tendinitis and tendon rupture in patients taking fluoroquinolones for systemic use. Fluoroquinolones are associated with an increased risk of tendinitis and tendon rupture. This risk is further increased in those

over age 60, in kidney, heart, and lung transplant recipients, and with use of concomitant steroid therapy. Physicians should advise patients, at the first sign of tendon pain, swelling, or inflammation, to stop taking the fluoroquinolone, to avoid exercise and use of the affected area, and to promptly contact their doctor about changing to a non-fluoroquinolone antimicrobial drug. Selection of a fluoroquinolone for the treatment or prevention of an infection should be limited to those conditions that are proven or strongly suspected to be caused by bacteria.

The FDA informed healthcare professionals of the risk of adverse injection site reactions in patients receiving naltrexone (Vivitrol®). Naltrexone is indicated for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment. Naltrexone is administered as an intramuscular gluteal injection and should not be administered intravenously, subcutaneously, or inadvertently into fatty tissue. Physicians should instruct patients to monitor the injection site and contact them if they develop pain, swelling, tenderness, induration, bruising, pruritus, or redness at the injection site that does not improve or worsens within two weeks. Physicians should promptly refer patients with worsening injection site reactions to a surgeon.

Numerous labeling changes were made to several drugs utilized within the facilities.

- A class effect for dystonia was added to: clozapine (Clozaril®), ziprasidone (Geodon®), haloperidol (Haldol®), haloperidol (Haldol®) decanoate, paliperidone (Invega®), quetiapine (Seroquel®), quetiapine XR.
- Aripiprazole (Abilify®) is reporting that lamotrigine (Lamictal®) has no clinically important drug interactions with aripiprazole.
- There has been postmarketing reports of toxic epidermal necrolysis with venlafaxine (Effexor®) and venlafaxine XR.
- Methylphenidate (Concerta®) received an indication for adults up to the age of 65 years old and added hypersensitivity to methylphenidate as a contraindication.
- Duloxetine (Cymbalta®) added an indication for fibromyalgia with a recommended dose of 60 mg/day. In addition, hepatotoxicity was added to the warnings and precautions section.
- Zolpidem (Ambien®) needs to be used with caution in patients with diseases or conditions that could affect metabolism or hemodynamic responses. The fact that angioedema and anaphylaxis has been reported with zolpidem has been added to the warnings and precautions section. In addition, abnormal thinking, behavioral changes and complex behaviors have been added as well. For drug interactions, information that the effect of inhibitors of other P450 enzymes has not been carefully evaluated has been added.
- Atomoxetine (Strattera®) added a maintenance dose for patients that are age 6-15 years with ADHD of 1.2 to 1.8 mg/kg/day after achieving a response based on a controlled trial. If a physician elects to use atomoxetine for extended periods, then the physician should periodically reevaluate the patient for long-term usefulness of the drug for that individual.

Survey of Child/Adolescent Dosing for Behavior Emergencies

At the last meeting, the “Treatment of Behavioral Emergencies Intramuscular Short-Acting Agents” for adults was approved. At that time, the Committee noted the lack of literature to support the identification of dosing of these medications for children and adolescents for behavior emergencies. As a result, a survey of the facilities regarding their dosing was initiated. At this time, not all facilities have returned their surveys. Since our facilities would offer a limited number of responses, it was suggested that other sources be contacted regarding the use of emergency medication in behavior emergencies. Dr. Becker and Dr. Hood will facilitate the gathering of additional information. Therefore, it was recommended that the review of this dosing be postponed until additional results can be obtained.

Therapeutic Optometrist Prescribing

Currently ophthalmic agents containing a steroid are restricted to consultation with an ophthalmologist prior to initiation. In Texas, therapeutic optometrists can also prescribe ophthalmic steroids. On a motion of Dr. Heidel, seconded by Dr. Becker, it was recommended that the guideline for use of ophthalmic agents containing a steroid be

changed to: "Consultation with an Ophthalmologist or Therapeutic Optometrist prior to initiation."

Atypical Antipsychotic Sectional Review

Dr. Mican presented the review of Atypical Antipsychotics. Some discussion focused on changing the name “Atypical” to “Second Generation” Antipsychotic. It was noted that for budget purposes, these types of drugs are referred to as “New Generation Medications” (New Gen Meds). All atypical antipsychotics are currently on Formulary except quetiapine (Seroquel®) XR. Quetiapine XR was reviewed in May 2008 and its addition to Formulary was denied. The table for the “Suggested Maximum Dose” was reviewed and no changes were recommended. The following items were presented to the Committee for discussion.

- Consider the removal of clozapine oral disintegrating tablet (Fazacllo®) from the Formulary
 - If clozapine oral disintegrating tablet remains on the Formulary, then consider adding Fazacllo® 12.5 mg
- Add risperidone long acting injection (Risperdal Consta®) 12.5 mg to the formulary
- Consider lowering the maximum adult dose for ziprasidone (Geodon®) to 200 mg per day

Due to pricing changes and the need for compliance with blood monitoring, the Committee discussed the removal of clozapine oral disintegrating tablet (Fazacllo®) from the Formulary. After an extensive discussion, it was decided to keep clozapine oral disintegrating tablet on Formulary. On a motion of Dr. Becker, seconded by Dr. Heidel, it was recommended to add Fazacllo® 12.5 mg tablet to the Formulary.

In reviewing the dosage strengths of the atypical antipsychotics that are formulary, it was recommended to add risperidone long acting injection (Risperdal Consta®) 12.5 mg to the Formulary. This would address the need for smaller doses in certain populations. On a motion of Dr. Becker, seconded by Dr. Heidel, it was recommended to add Risperdal Consta® 12.5 mg to the Formulary.

There was some discussion on whether or not the maximum dose of ziprasidone should be reduced. The maximum dose of ziprasidone is listed as 240 mg/day but the package insert states that the maximum dose is 200 mg/day. The maximum dose of 240 mg was previously established because of the capsule sizes as it is difficult to reach 200 mg/day without increasing the daily cost of the medication. Therefore, 240 mg was previously selected as the maximum dose. On a motion of Dr. Hood, seconded by Ms. Millhollon, it was recommended that the maximum dose of ziprasidone remain at 240 mg/day.

The atypical antipsychotic audit criteria were reviewed. The following changes were recommended for clozapine (Clozaril®, Fazacllo®);

- For Precaution – add “dementia-related psychosis”
- For Drug Interactions of Major Significance – add “clozapine is a major substrate of CYP 1A2 and a moderate inhibitor of CYP 2D6”
- For Side Effects Which Require Medical Attention – add “Pulmonary embolism or DVT, Hepatitis, Cardiomyopathy/myocarditis”

The following changes were recommended for the other atypical antipsychotics:

- Add paliperidone (Invega®) to the listing of atypical antipsychotics
- For Indication – add “bipolar disorder; augmentation agent for MDD (aripiprazole)”
- For Precautions – add “dementia-related psychosis, renal impairment (paliperidone and ziprasidone injection)”
- For Drug Interactions of Major Significance – add “the following are the major metabolic pathways for the atypical antipsychotics: risperidone CYP 2D6, olanzapine CYP 1A2, quetiapine CYP3A4, aripiprazole CYP 2D6 and 3A4, ziprasidone (aldehyde oxidase), paliperidone (non-hepatic, primarily renal elimination)”
- For Side Effects Which Require Medical Attention – add paliperidone to galactorrhea, amenorrhea and gynecomastia; add “hyperlipidemia” to the list of side effects

On a motion of Dr. Heidel, seconded by Ms. Millhollon, the audit criteria changes were approved.

In addition, all antipsychotics will need to have “dementia-related psychosis” added as a precaution.

Non-Formulary Dosage Strength Additions

In reviewing a listing of non-formulary drugs in WORx, Dr. Richards recommended that the following dosage strengths be added to the Formulary. For these items, other dosage strengths of the drug are currently on Formulary.

- Amino Acid Injection
 - With dextrose/electrolytes: 2.75%, 4.25%, 5%
 - Trade Name – Clinimix E
- Abrasive Cleaner
 - Trade Name – Seba-Nil
- Activated Charcoal
 - Capsule: 200 mg, 260 mg; Tablet: 260 mg
- Albuterol/ipratropium
 - Solution, inhalation: 2.5 – 0.5 mg/3 ml
 - Trade Name – Duoneb
- Azithromycin
 - Tablet: 500 mg
- Beclomethasone
 - Inhaler, oral: 40 mcg (100 actuations), 80 mcg (100 actuations)
- Betamethasone dipropionate
 - Cream: 0.05%
 - Gel: 0.05%
 - Ointment: 0.05%
- Emollient Gel
 - Gel, topical:
 - Trade Name – Clinac O.C.
- Estrogen/medroxyprogesterone (PremPro)
 - Tablet: Conjugated estrogen 0.625 mg – medroxyprogesterone 5 mg
 - Tablet: Conjugated estrogen 0.45 mg – medroxyprogesterone 1.5 mg
 - Tablet: Conjugated estrogen 0.3 mg – medroxyprogesterone 1.5 mg
 - Add Trade name – Premphase
- Fluorescein Sodium
 - Strip, ophthalmic: 0.6 mg
- Galantamine
 - Capsule, 24H: 8 mg, 16 mg, 24 mg
 - Solution: 4 mg/ml
- Guaifenesin – pseudoephedrine
 - Delete Entex PSE trade name
 - Change strengths from Guaifenesin 600 mg – pseudoephedrine 120 mg to 600 mg and 60 mg
 - Trade Name – Mucinex D
- Mirtazapine
 - Tablet: 7.5 mg
- Salicylic acid
 - Cleaning pads
 - Gel, topical: 6%
- Salicylic acid – sulfur
 - Cleanser
 - Cream
 - Lotion
 - Gel
- Tizanidine – Reserve Use
 - Capsule: 6 mg
- Vitamin B Complex
 - Tablet: each tablet contains a minimum of USDA requirements

On a motion of Dr. Heidel, seconded by Ms. Millhollon, it was recommended that these dosage strengths be added to the Drug Formulary.

Quarterly Non-Formulary Drug Justification Report

In reviewing the third quarter's non-formulary drug purchases, it was noted that carvedilol (Coreg®) is being requested frequently. It was recommended that carvedilol be reviewed at the next meeting.

The Committee discussed the possibility of adding loratadine/pseudoephedrine (Claritin-D®) and pramoxine/camphor/zinc acetate (Caladryl Clear®) to the Formulary. Each component of Claritin-D® is currently on Formulary and this product is currently available generically. The Caladryl Clear® is similar to Caladryl® except for the calamine, so this product does not have a pink appearance. On a motion of Dr. Mican, seconded by Dr. Becker, the recommendation to add Claritin-D® and Caladryl Clear® to the Formulary was approved.

Drug Formulary Sectional Review-Cardiovascular Agents

Dr. Tramonte was not available to provide the Cardiovascular Agent Review.

Sectional Review for Next Meeting

The cardiovascular agents will be reviewed at the next meeting.

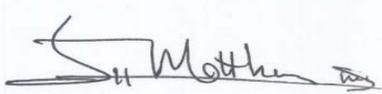
Next Meeting Date

The next meeting was scheduled for December 5, 2008.

Adjourn

There being no further business, the meeting was adjourned at 12:50 p.m.

Approved: _____


Jeff R. Matthews, M.D., Chairman

Attachments

Attachment A – New Drug Applications

Minutes Prepared by:

Ann L. Richards, Pharm.D., BCPP

Appendix 1: New Drug Application Form

TEXAS DEPARTMENT OF MENTAL HEALTH AND MENTAL RETARDATION

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

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

Date: June 5, 2008

Name of practitioner submitting the application: Dr. Sylvia Muzquiz-Drummond

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)):

MHMRA of Harris County

Information regarding new drug:

Therapeutic Classification	Long Action Pro-Drug Stimulent
Generic Name	lisdexamfetamine dimesylate
Trade Name(s)	VYVANSE™
Manufacturer(s)	Shire
Dosage Form(s)	Capsule

Explain the pharmacological action or use of this drug: Vyvanse is a pro-drug of dextroamphetamine. It works primarily by inducing the release of the neurotransmitters dopamine and norepinephrine from their storage areas in nerve terminals. Both of these transmitters contribute to maintaining alertness, increasing focus, and sustaining thought, effort, and motivation.

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

Many individuals that are seen in our system as kids with ADHD and BIPOLAR/Depression or Schizophrenia go into our adult system who do not get treated for their ADHD by the adult MDs because there really is not a treatment indicated for Adult ADHD. See Medscape article below.

State which drugs this new drug would replace or supplement:

None

Developed under the direction and sponsorship of Shire

FDA Approves VYVANSE™ (lisdexamfetamine dimesylate), the First and Only Once-Daily Prodrug Stimulant to Treat ADHD in Adults



Within the first eight months since its introduction in the United States, VYVANSE has achieved over one million prescriptions

In a clinical study with adults, VYVANSE was shown to significantly improve the symptoms of ADHD (inattention, hyperactivity and impulsivity)¹

Basingstoke, U.K. and Philadelphia, PA - April 23, 2008- Shire plc (LSE: SHP, NASDAQ: SHPGY), the global specialty biopharmaceutical company, today announced that it has received approval from the U.S. Food and Drug Administration (FDA) for VYVANSE™ (lisdexamfetamine dimesylate), for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults. VYVANSE, introduced in July 2007 for the treatment of ADHD in children aged 6 to 12 years, is now the first and only once-daily prodrug stimulant approved to treat adults with ADHD. In its first eight months of availability, more than one million VYVANSE prescriptions have been filled.²

"We are very pleased with this FDA approval of the adult indication for VYVANSE," said Matthew Emmens, Chief Executive Officer of Shire. "This approval provides physicians a new treatment option that can help their adult patients by significantly improving their ADHD symptoms. VYVANSE has been well accepted by the medical community. With Shire's experience as a leader in the development and commercialization of ADHD medications, we are confident that this approval for adult patients will help continue to increase prescription share and volume of VYVANSE."

"Many people may think of ADHD as only a childhood disorder but the fact is that the majority of children diagnosed with ADHD still have symptoms as an adult. These symptoms can significantly impact them at work, home and in relationships, where they have important responsibilities," said David W. Goodman, assistant professor of psychiatry and behavioral sciences at Johns Hopkins University School of Medicine and director of the Adult Attention Deficit Disorder Center of Maryland. "The good news is that in a clinical study with adults, one daily dose of VYVANSE significantly improved ADHD symptoms of inattention, such as the ability to focus and organize, as well as hyperactivity and impulsivity."

Since VYVANSE became available for children with ADHD in July 2007, the product has achieved a U.S. market share of 6.9 percent based on weekly branded prescription volume. VYVANSE formulary coverage has been positive, with the top six managed care plans now covering the product in a preferred formulary position.

VYVANSE is a therapeutically inactive prodrug, in which *d*-amphetamine is covalently bonded to l-lysine, and after oral ingestion it is converted to pharmacologically active *d*-amphetamine.³ The conversion of VYVANSE to *d*-amphetamine is not affected by gastrointestinal pH and is unlikely to be affected by alterations in normal GI transit times.⁴

VYVANSE is currently available in three dosage strengths of 30 mg, 50 mg and 70 mg, each for once-daily dosing. Additional dosage strengths of 20 mg, 40 mg and 60 mg VYVANSE have also been FDA-approved and are expected to be available in pharmacies this summer.

Additional information about VYVANSE and Full Prescribing Information are available at www.vyvance.com.

VYVANSE Significantly Improved ADHD Symptoms

The phase III pivotal trial that led to the FDA approval of VYVANSE to treat adults with ADHD was a double-blind, placebo-controlled, four-week study with dose escalations in 414 adults aged 18 to 55 years. In this study, adults with ADHD experienced significant improvements in ADHD symptom control within one week of treatment with once-daily VYVANSE.¹

Treatment with VYVANSE at all doses studied (30 mg, 50 mg, 70 mg) was significantly more effective than placebo, providing a reduction in ADHD Rating Scale (ADHD-RS-IV) scores ranging from 16.2 to 18.6 points at endpoint.¹ The ADHD-RS-IV is a standardized test for assessing symptoms of ADHD and for assessing their response to treatment.^{5,6} This scale, which contains 18 items, is based on the ADHD diagnostic criteria as defined in the APA's *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision[®], a publication of the American Psychiatric Association.⁷

Investigators also measured the efficacy of VYVANSE with the Clinical Global Impressions-Improvement (CGI-I) scale and found that the percentage of subjects taking VYVANSE that rated improved ranged from 57 to 61 percent across all doses and was significantly greater than placebo.¹ The CGI-I scale is a standard assessment used to rate the severity of a patient's illness and improvement over time.⁸

The most commonly reported adverse events in this study were decreased appetite, difficulty falling asleep, and dry mouth.

About ADHD

ADHD is one of the most common psychiatric disorders in children and adolescents.⁹ Approximately 7.8 percent of all school-aged children, or about 4.4 million U.S. children aged 4 to 17 years, have been diagnosed with ADHD at some point in their lives, according to the U.S. Centers for Disease Control and Prevention (CDC).¹⁰ The disorder is also estimated to affect 4.4 percent of U.S. adults aged 18-44 based on results from the National Comorbidity Survey Replication, a nationally representative household survey, which used a lay-administered diagnostic interview to assess a wide range of DSM-IV disorders.¹¹ ADHD is a neurobiological disorder that manifests as a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development.⁷ To be

properly diagnosed with ADHD, a child needs to demonstrate at least six of nine symptoms of inattention; and/or at least six of nine symptoms of hyperactivity/impulsivity; the onset of which appears before age 7 years; that some impairment from the symptoms is present in two or more settings (e.g., at school and home); that the symptoms continue for at least six months; and that there is clinically significant impairment in social, academic or occupational functioning and the symptoms cannot be better explained by another psychiatric disorder.⁷

Although there is no "cure" for ADHD, there are accepted treatments that specifically target its symptoms. The most common standard treatments include educational approaches, psychological or behavioral modification, and medication.¹²

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Notes to editors

About VYVANSE

Tell the doctor about any heart conditions, including structural abnormalities, that you, your child, or a family member, may have. Inform the doctor *immediately* if you or your child develops symptoms that suggest heart problems, such as chest pain or fainting.

Vyvanse should not be taken if you or your child has advanced disease of the blood vessels (arteriosclerosis); symptomatic heart disease; moderate to severe high blood pressure; overactive thyroid gland (hyperthyroidism); known allergy or unusual reactions to drugs called sympathomimetic amines (for example, pseudoephedrine); seizures; glaucoma; a history of problems with alcohol or drugs; agitated states; taken a monoamine oxidase inhibitor (MAOI) within the last 14 days.

Tell the doctor *before* taking Vyvanse if you or your child is being treated for or has symptoms of depression (sadness, worthlessness, or hopelessness) or bipolar disorder; has abnormal thought or visions, hears abnormal sounds, or has been diagnosed with psychosis; has had seizures or abnormal EEGs; has or has had high blood pressure; exhibits aggressive behavior or hostility. Tell the doctor *immediately* if you or your child develops any of these conditions or symptoms while taking Vyvanse.

Abuse of amphetamines may lead to dependence. Misuse of amphetamine may cause sudden death and serious cardiovascular adverse events. These events have also been reported rarely with amphetamine use.

Vyvanse was generally well tolerated in clinical studies. The most common side effects reported in studies of Vyvanse were: *children* - decreased appetite, difficulty falling asleep, stomachache, and

irritability; *adult* - decreased appetite, difficulty falling asleep, and dry mouth.

Aggression, new abnormal thoughts/behaviors, mania, growth suppression, worsening of motion or verbal tics, and Tourette's syndrome have been associated with use of drugs of this type. Tell the doctor if you or your child has blurred vision while taking Vyvanse.

SHIRE PLC

Shire's strategic goal is to become the leading specialty biopharmaceutical company that focuses on meeting the needs of the specialist physician. Shire focuses its business on attention deficit and hyperactivity disorder (ADHD), human genetic therapies (HGT), gastrointestinal (GI) and renal diseases. The structure is sufficiently flexible to allow Shire to target new therapeutic areas to the extent opportunities arise through acquisitions. Shire's in-licensing, merger and acquisition efforts are focused on products in niche markets with strong intellectual property protection either in the US or Europe. Shire believes that a carefully selected portfolio of products with strategically aligned and relatively small-scale sales forces will deliver strong results.

For further information on Shire, please visit the Company's website: www.shire.com.

"SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

Statements included herein that are not historical facts are forward-looking statements. Such forward-looking statements involve a number of risks and uncertainties and are subject to change at any time. In the event such risks or uncertainties materialize, Shire's results could be materially affected. The risks and uncertainties include, but are not limited to, risks associated with: the inherent uncertainty of pharmaceutical research, product development including, but not limited to the successful development of JUVISTA® (Human TGFβ3) and veleglucerase alfa (GA-GCB); manufacturing and commercialization including, but not limited to, the establishment in the market of VYVANSE™ (lisdexamfetamine dimesylate) (Attention Deficit and Hyperactivity Disorder ("ADHD")); the impact of competitive products, including, but not limited to, the impact of those on Shire's ADHD franchise; patents, including but not limited to, legal challenges relating to Shire's ADHD franchise; government regulation and approval, including but not limited to the expected product approval date of INTUNIV™ (guanfacine extended release) (ADHD); Shire's ability to secure new products for commercialization and/or development; and other risks and uncertainties detailed from time to time in Shire plc's filings with the Securities and Exchange Commission, including Shire plc's Annual Report on Form 10-K for the year ended December 31, 2007.

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application is approved

signature of chairman of facility pharmacy and therapeutics committee

OR

application is appropriate and complete

signature of clinical/medical director or designee

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EXHIBIT A

APPENDIX 1: NEW DRUG APPLICATION FORM

TEXAS DEPARTMENT OF MENTAL HEALTH AND MENTAL RETARDATION

NEW DRUG APPLICATION
(for inclusion in the DSHS/DADS Drug Formulary)

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

Date: 7-31-08

Name of practitioner submitting the application: Dr. Matthew Bramson

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)):

Texas MHMR, Harris County MHMR

Information regarding new drug:

Therapeutic Classification	Stimulants
Generic Name	Dex-methylphenidate XR
Trade Name(s)	Focalin XR
Manufacturer(s)	Novartis
Dosage Form(s)	5, 10, 15, 20

Explain the pharmacological action or use of this drug: Dopamine and Norepinephrine reuptake inhibitor

Explain the advantages of this drug over those listed in the formulary: Improved tolerability profile especially Irritability, insomnia, TICS (See enclosed DATA), Clinical experience shows focalin XR better tolerated with ADHD + comorbidities (Anxiety, Bipolar, Tourette).
State which drugs this new drug would replace or supplement: metadate CD, Ritalin LA →

Focalin XR has ~15% market share in Texas - It is commonly the only stimulant that a child can tolerate but availability is not there.

M. Bramson

application is approved

signature of chairman of facility pharmacy and therapeutics committee

OR

application is appropriate and complete

M. Bramson

signature of clinical/medical director or designee

