DADS/DSHS EXECUTIVE FORMULARY COMMITTEE MINUTES
June 22, 2007

The Executive Formulary Committee convened on Friday, June 22, 2007 in Conference Room 164 - CO Building 2. The meeting was called to order by Dr. Ward, Interim Chair at 9:58 a.m.

Janet Adams, MSN, RN, CNS	Absent	Mike Maples	Absent
Rosha Chadwick, R.Ph.	Absent	Michael Woolsey	Absent
Jeanna Heidel, Pharm.D.	√	Jay Norwood, MSN, RN	Absent
J. Brett Hood, M.D.	√	Camille Hemlock, M.D.	Absent
Lisa Mican, Pharm.D.	√	Nina Muse, M.D.	Absent
Connie Millhollon, RN,	Absent	Vacant Medical Director Position	
Victoria B. Morgan, M.D.	Absent	Vacant Center Position	
Ann L. Richards, Pharm.D.	√	Vacant Center Position	
Bernardo C. Tarin-Godoy, M.D.	Absent	Vacant Center Position	
Robert L. Ward, D.O.	√	Vacant State School Position	
Kenny Dudley	Absent	Mark Jeffers	

Guest Present: Sharon Tramonte, Pharm.D., San Antonio State School; Richard Perry, Pharm.D., Resident; Jill Fowler, Pharm.D., Resident

Approval of Minutes of February 16, 2007

On a motion of Dr. Mican, seconded by Dr. Hood, the minutes of the February 16th 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 22-year old male was previously treated with clozapine (Fazaclo®) oral disintegrating tablets (ODT) without any problems regarding his WBC or ANC. On the next admission, the patient was placed back on clozapine ODT and was titrated to 700 mg/day. Later, lamotrigine (Lamictal®) was added to the patient's regimen and the dose was titrated to 50 mg/day. Immediately prior to the initiation of the lamotrigine, the patient had a WBC of 5,700/mm^3 and an ANC of 3,700/mm^3. Approximately 20 days after the initiation of the lamotrigine, the WBC was 5,300/mm^3 with an ANC of 1,900/mm^3. A second CBC was drawn three days later and the WBC was 3,900/mm^3 with an ANC of 1,000/mm^3. The clozapine ODT was discontinued and daily CBCs were obtained. Overall, the WBC and ANC continued to drop. The lamotrigine was discontinued four weeks after initiation. Filgrastim (Neupogen®) was ordered on a daily basis. After two doses the patient's CBC was 24,400/mm^3 with an ANC of 17,812/mm^3. The filgrastim was discontinued and the WBC/ANC normalized within two weeks.
In the second case, a 23- year old male was admitted to a psychiatric facility. Nine days after admission, the patient

was started on clozapine (Fazaclo®) oral disintegrating tablets (ODT). The patient experienced excessive sedation. Fifteen days after clozapine initiation, the patient complained of tiredness and was experiencing labored breathing. The patient had a pulse of 142 and a heart rate of 147. A troponin I level was significantly elevated 0.73 ng/ml at 9:35 am on 1/23/07. The clozapine was discontinued and the patient was transferred to a medical facility. At the medical facility, the patient was diagnosed with hypoxemia secondary to ARDS, MRSA pneumonia and sepsis. The patient was treated with vancomycin and put on a ventilator. The patient returned to the psychiatric facility on 2/11/07 with all serious medical issues resolved.

A 15-year old male with schizoaffective disorder bipolar type and conduct disorder was admitted to a state hospital. The patient also had mild mental retardation, Williams Syndrome, obesity and hypothyroidism. The outpatient medications were continued upon admission. These include: oxcarbazepine (Trileptal®) 600 mg BID, quetiapine (Seroquel®) 800 mg HS, divalproex (Depakote®) 750 mg BID, benztropine (Cogentin®) 1 mg BID, levothyroxine (Synthroid®) 0.1 mg daily and propranolol (Inderal®) 40 mg daily. The admission CBC showed a WBC of 3,400/mm^3 and an ANC of 1,000/mm^3. The oxcarbazepine was decreased to 300 mg BID for three days and then discontinued. The other medications continued as written with the exception of an increase in divalproex. Repeat CBCs showed an improvement in both the WBC and ANC. In reviewing this adverse drug reaction, Dr. Mican reported that empirically adolescents tend to have more problems with a decreased in WBC/ANC with quetiapine, oxcarbazepine and divalproex than adults. The review of this issue is currently being considered for a resident project. Waco Center for the Youth will be contacted to see if they have noticed an increase in this adverse effect.

A 33-year old male was admitted to a state hospital on 10/12/06 for the treatment of schizoaffective disorder. The patient had been treated with ziprasidone (Geodon®) and carbamazepine (Tegretol®) prior to the admission. The ziprasidone was continued and the carbamazepine was discontinued. Baseline liver function tests were within normal limits. The patient was started on bupropion (Wellbutrin®) SR 150 mg AM and divalproex (Depakote®) ER 1,500 mg HS. Duloxetine (Cymbalta®) 30 mg daily was initiated on 10/18/06. On 10/20/06, the liver function tests were noted to be elevated so the bupropion SR was discontinued. Three days later, the liver function tests were still elevated. On 10/24/06, the divalproex ER was discontinued. On 10/26/06 the liver function tests were still elevated but they began to normalize on 10/30/06.

An 18-year old male was admitted to a state hospital on 9/6/06 and was treated with quetiapine (Seroquel®) 1,500 mg daily and divalproex (Depakote®) ER 1,000 mg daily. The divalproex ER dose was increased to 1,500 mg on 9/11/06. The patient was discharged and later readmitted to the hospital on 10/21/06. On this admission, divalproex ER 2,000 mg daily and quetiapine 1,200 mg were prescribed. On 11/22/06, the quetiapine dose was increased to 1,500 mg. Patient expired on 12/12/06, approximately 12 hours after the onset of the following symptoms: diarrhea, abdominal pain and drowsiness. This was 36 hours after the initial symptoms of poor appetite, indigestion and constipation. The patient was transferred to an emergency room prior to his death. The autopsy lists the cause of death as acute hemorrhagic necrotizing pancreatitis with extensive surrounding fat necrosis.

A 20-year old female employee received hepatitis B vaccine (Recombivax® HB) in the shoulder. Approximately 1 ½ hours later the employee complained of pain in her arm. The arm began to swell up and become hard. She was unable to move her arm. She received sulfamethoxazole/trimethoprim (Bactrim®) and hydrocodone/acetaminophen (Vicodin®) as treatment. The reaction dissipated over one week.

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 TIMA Procedural Manual for the Schizophrenia Module was last updated in 2003. Dr. Crismon reports that the module should be updated soon. Dr. Tramonte noted that the Schools are considering changing their required monitoring.

Psychotropic Dosing in Children and Adolescents

Dr. Mican presented the recommendations for maximum doses for sedative/hypnotic agents in children and adolescents. She noted that these medications are being used in this patient population but that there are an inadequate number of studies showing effectiveness. Information obtained from a survey of community-based pediatricians reports that non-prescription and prescription medication are being prescribed in this patient

population. The following is a summary of the drugs reviewed.

Amobarbital (Amytal®) - No recommended maximum dose was made as barbiturates are not recommended in the pediatric population due to unacceptable adverse effects.

Chloral hydrate (Noctec®) - It was noted that most of the pediatric literature addresses the use of chloral hydrate in pre-procedure sedation versus insomnia. A PubMed search found no controlled clinical trials evaluating the use of chloral hydrate for insomnia in pediatric patients. It was recommended that the chloral hydrate dose for pre-procedure sedation be listed in the table for children and adolescents with a notation that the recommended maximum dose is for pre-procedure sedation only. The maximum pre-procedure sedation dose for children (6-12 year old) is 50 mg/kg up to 1,000 mg and the maximum pre-procedure sedation dose for adolescents (13-17 years old) is 1,000 mg.

Diphenhydramine (Benadryl®) – A recent survey of community-based pediatricians reported antihistamines to be the most commonly recommended non-prescription medication for pediatric insomnia. It was recommended that the maximum dose in children is 1 mg/kg up to 50 mg with a maximum daily dose of 300 mg and the maximum dose in adolescents is 50 mg with a maximum daily dose of 300 mg.

Hydroxyzine (Vistaril®, Atarax®) – There is limited data available regarding the use of hydroxyzine for insomnia. There are several controlled clinical trails demonstrating the efficacy of hydroxyzine in pre-procedure sedation with variable dosing in conjunction with midazolam (Versed®), meperidine (Demerol®) and chloral hydrate (Noctec®). One study showed that the combination of hydroxyzine and chloral hydrate lead to high rates of oxygen desaturations and deep sedation. It was recommended that the maximum dose for children is 2 mg/kg up to 100 mg with a maximum daily dose of 100 mg and for adolescents the maximum dose and maximum total daily dose be 100 mg.

Temazepam (Restoril®) – In the recent survey of community based pediatricians, 11.9% reported prescribing at least one prescription for a benzodiazepine for pediatric insomnia in the last 6 months. Benzodiazepines used for pediatric insomnia can result in residual daytime sedation, impairment of psychomotor performance, disinhibition, nausea and vomiting. A PubMed search found no controlled trials utilizing temazepam as an agent for insomnia in children or adolescents. Limited information was available regarding the use of temazepam for pre-procedure sedation. Due to the lack of information available on treating children and adolescents with temazepam, a maximum suggested dose cannot be established.

Trazodone (Desyrel®) – Based on a prior meeting, the recommended maximum dose per day for children is 100 mg and for adolescents it is 200 mg. It was recommended that the maximum adult dose be increased to 200 mg per day.

Triazolam (Halcion®) – As previously mentioned, the community based survey reported that 11.9% of the pediatricians had prescribed one benzodiazepine in the previous six months for pediatric insomnia. The side effects listed for temazepam are applicable to triazolam. There is limited information regarding triazolam use in pediatrics. A few studies have been conducted looking at the use of triazolam as an oral sedative prior to dental procedures. With limited information available regarding the use of triazolam in children and adolescents, a maximum suggested dose cannot be established.

Zaleplon (Sonata®) – There are no published clinical studies found regarding its use in children and adolescents. The manufacturer was contacted on June 18, 2007 and reported no data on file regarding zaleplon use in children and adolescents. Zaleplon has not been studied regarding safety and efficacy in the child and adolescent population so no maximum dose has been established.

Zolpidem (Ambien®) – An 8-week randomized, placebo-controlled study was conducted in 201 pediatric patients aged 6-17 years with insomnia and ADHD. Patients were treated with oral zolpidem (0.25 mg/kg/day) up to a maximum of 10 mg/day (n=136) or placebo (n=65). Zolpidem did not significantly decrease sleep latency to persistent sleep compared to placebo, as measured by polysomnography after 4 weeks of treatment. Psychiatric and nervous system disorders were more frequent with zolpidem versus placebo (23.5% vs. 1.5%). Hallucinations were reported in 7.4% of the pediatric patients receiving zolpidem versus 0% in placebo. It was noted that the incidence of

hallucinatory experiences was higher in the age group under 12 years old compared to those over 12 years old. Zolpidem is not recommended for use in children. Due to the potential for psychiatric and nervous system disorders including hallucinations, it was not recommended for use in adolescents.

On a motion of Dr. Hood, seconded by Dr. Heidel, the Sedative Hypnotics Agents: Child & Adolescent Suggested Maximum Formulary Doses were approved as modified. See Attachment A.

FDA Alerts

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

For rosiglitazone (Avandia®), the FDA provided an alert in which they acknowledged their awareness of a potential safety issue related to rosiglitazone. Safety data from a pooled analysis of controlled clinical trials have shown a significant increase in the risk of heart attack and heart-related deaths in patients taking rosiglitazone. However, other published and unpublished data from long-term clinical trials of rosiglitazone provide contradictory evidence about the risk of ischemic cardiovascular events in patients taking rosiglitazone. FDA's review of all available data is ongoing. FDA has not confirmed the clinical significance of the reported increased risk of ischemic cardiovascular events in the context of other studies. Myocardial ischemic events are currently described in the WARNINGS section of the rosiglitazone label. The FDA does not know whether the other approved medications in the same pharmacologic class or other oral drugs treating type 2 diabetes have less, the same or greater risks. Switching diabetic patients to other therapies also confers its own risks. For those reasons, the FDA is providing this emerging information to prescribers so that they and their patients can make individualized treatment decisions.

The FDA noted that these warnings can be found in the current prescribing information available at: http://www.fda.gov/cder/foi/label/2007/021071s023lbl.pdf

The FDA recommends that health care professionals consider this and other available data when making individual treatment decisions for their patients with type 2 diabetes.

Quarterly Non-Formulary Drug Justification Report

The Quarterly Non-Formulary drug list was reviewed by facility and generic name. A few facilities are not reporting all the non-formulary drug requests. It was requested that a follow up contact be made for those facilities that are not reporting on a consistent basis.

ADHD Drug Review

Dr. Mican presented an ADHD stimulant medication sectional review. The current drug formulary has the following listing for stimulants:

Amphetamine Mixture (Adderall, Adderall XR) C-II
- Capsule, extended release: 5mg, 10mg, 15mg, 20mg, 25mg, 30mg
- Tablet: 5mg, 10mg, 12.5mg, 15mg, 20mg, 25mg, 30mg

Atomoxetine (Strattera)
- Capsule: 10mg, 18mg, 25mg, 40mg, 60mg

Dextroamphetamine (Dexedrine) C-II
- Capsule, sustained release: 5mg, 10mg, 15mg
- Tablet: 5mg, 10mg

Methylphenidate (Ritalin, Concerta) C-II
- Tablet: 5mg, 10mg, 20mg
- Tablet, extended release: 18mg, 36mg, 27mg, 54mg
- Tablet, sustained release: 20mg

Dr. Mican made the following recommendations regarding the Formulary listing:

- For amphetamine mixture, add the 7.5 mg tablet
- For amphetamine mixture, delete the 25 mg immediate release tablet as it is not available
- For atomoxetine, add the 80 mg and 100 mg capsules
- For dextroamphetamine, add the trade names Dexedrine® Spansules and Dextrostat® to the listing
- Divide the methylphenidate listing into two separate listings. One for immediate release and the other for extended release. Include the respective trade names for each listing.
- For methylphenidate immediate release, add the trade names Methylin® and Metadate®

On a motion of Dr. Heidel, seconded by Dr. Ward, these recommendations were approved.

Dr. Mican and colleagues reviewed the new drug applications for the treatment of ADHD. This information is presented in the New Drug Applications Section.

New Drug Applications

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

Lisdexamfetamine (Vyvanse®) - discussed by Dr. Perry

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. The mode of therapeutic action in ADHD is not known. 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*. It is indicated in the treatment of ADHD in children aged 6 to 12 years. Lisdexamfetamine has comparable efficacy, safety and cost to the mixed amphetamine salt (Adderall®) XR and is about seven times as expensive for daily treatment as immediate release mixed amphetamine salts. The studies reported use of previous responders to treatment and those without co-morbid psychiatric illness, which is not representative of the institutions' patient population. Currently, there are no published studies regarding the abuse potential and thus it can not be evaluated. There is no short acting version of lisdexamfetamine available.

Based on a lack of a motion, the request to add lisdexamfetamine (Vyvanse®) to the Formulary was denied.

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

Dexmethylphenidate is the pharmacologically *d-threo* enantiomer of racemic methylphenidate (Ritalin®). Dexmethylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neurons and increase the release of these monoamines into the extraneuronal space. The dexmethylphenidate extended release product used the proprietary SODAS® (Spheroidal Oral Drug Absorption System) technology. Each capsule contains half immediate-release beads and half enteric-coated, delayed-release beads. Dexmethylphenidate extended release is indicated for the treatment of ADHD in patients aged 6 years and older. To date, safety and efficacy comparisons between dexmethylphenidate extended release and methylphenidate (Ritalin®) have not been completed. Currently, only pharmacokinetic comparisons with methylphenidate have been conducted for dexmethylphenidate extended release. Studies are not available to conclude if dexmethylphenidate extended release provides a superior drug profile in regard to safety, tolerability and efficacy with any formulation of methylphenidate. The Drug Formulary does not currently include the dexmethylphenidate immediate release product.

Based on a lack of a motion, the request to add dexmethylphenidate extended release (Focalin® XR) to the Formulary was denied.

Methylphenidate extended release capsules (Metadate® CD) - discussed by Dr. Mican

Methylphenidate 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. Methylphenidate is a racemic mixture, the *d-threo* enantiomer is more pharmacologically active than the *l-threo* enantiomer. The extended-release capsules comprise both immediate-release (IR) - 30% and extended-release (ER) - 70% beads. Methylphenidate extended release is indicated in the treatment of ADHD in patients aged 6 and older. Metadate® CD is administered once daily in the morning, before breakfast. The capsule may be swallowed whole or opened up and sprinkled into small amounts of apple sauce and given immediately. The initial dose is 20 mg/day and may be adjusted in 10-20 mg increments to a maximum of 60 mg/day in the morning.

Following discussion, on motion of Dr. Mican, seconded by Dr. Heidel, the request to add methylphenidate extended release (Metadate® CD) to the formulary was approved. The Formulary CheckList was completed.

Ramelteon (Rozerem®) - discussed by Dr. Fowler

Ramelteon is a melatonin receptor agonist which selectively binds melatonin MT_1 and MT_2 receptors in the suprachiasmatic nucleus of the hypothalamus, with little affinity for the MT_3 receptor. Activation of MT_1 and MT_2 receptors by endogenous melatonin is believed to be involved in generation of the circadian rhythm underlying the normal sleep-wake cycle. The MT_1 receptor is believed to be involved in producing sleepiness, while the MT_2 receptor is thought to be involved in phase-shifting effects on the circadian rhythm. Ramelteon has a greater affinity and selectivity for MT_1 receptors compared with melatonin, which would theoretically offer an advantage over melatonin in the treatment of sleep-onset insomnia. While total absorption is at least 84%, the absolute bioavailability is low (1.8%) due to extensive first-pass metabolism. Ramelteon is indicated for the treatment of insomnia characterized by difficulty with sleep onset. The recommended dose is 8 mg taken within 30 minutes of going to bed. Precautions with the use of ramelteon includes: decreased testosterone levels and increased prolactin levels which have been associated with use in adults. Ramelteon is the only FDA-approved prescription medication for the treatment of insomnia that is not a controlled substance. The primary advantages of ramelteon appear to be its lack of abuse potential and safety profile. Decreases in sleep latency with ramelteon compared to placebo in clinical trials were small, ranging from 7.6 to 13.4 minutes for ramelteon 8 mg. In addition to the seemingly small treatment effect, ramelteon is much more expensive than other commonly used treatments for insomnia. The net cost difference between one dose of ramelteon 8 mg and zolpidem 10 mg or trazodone 100 mg is about $2.50.

Based on a lack of a motion, the request to add ramelteon (Rozerem®) to the Formulary was denied.

Proposed Drug Deletion List -

Otic Agents
Nasal, Mouth and Throat Agents
Irrigation Solutions

The Committee did not receive any comments from the field about the proposed deletions for the otic agents; nasal, mouth and throat agents and irrigation solutions. On a motion of Dr. Ward, seconded by Dr. Heidel, the motion to delete these agents was approved.

Pharmaceutical Waste

Dr. Richards noted that in reviewing the Pharmacy OI, it was noted that tablets or capsules that are contaminated in the care area should be destroyed in the care area. For a controlled substance, the tablet or capsule should be destroyed by placing it in a sharps container or in the waste water system and this destruction shall be witnessed. Inhalers, creams, solutions, and ointments that are contaminated (in contact with bodily fluids), shall be returned to the Pharmacy in a resealable bag. Contaminated drugs that are returned to the Pharmacy shall be destroyed by a waste management company approved for drug destruction. If the disposal system does not accept contaminated drugs in aerosol containers, then they must be rendered useless and placed in the trash. Dr. Richards completed a survey of the Pharmacy Directors regarding waste management companies. For the ten facilities that have already responded, all ten facilities use a waste management company and all ten report that the company takes all medications including patient-dispensed medications. It appears that the facilities have the necessary resources to complete the destruction of medication.

Drug Formulary Sectional Review- Dermatological Agents, Part 1

Due to time constraints the sectional review of Dermatological Agents was not available for the meeting.

Sectional Review for Next Meeting

The first part of dermatological agents will be reviewed at the next meeting.

Miscellaneous Items

The Committee discussed the use of video-conferencing for the meeting. It was noted that the School representatives do not necessarily have access to this technology. Dr. Ward noted that the personal face-to-face interaction is very important in conducting the business of the Committee. Therefore, this appears to not be a viable option at this time.

Apparently some of the Clinical Directors expressed interest in participating in the Committee meetings. As always, any Clinical Director can attend a meeting by notifying either Sally D. Smith, Dr. Richards or Dr. Ward in advanced and by attending the meeting in person.

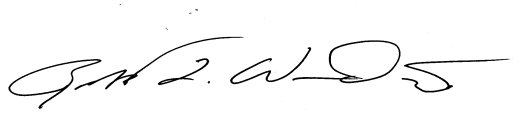
Next Meeting Date

The next meeting was scheduled for October 12, 2007.

Adjourn

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

APPROVED:



Robert Ward, D.O., Interim Chairman

Attachments

Attachment A – Sedative Hypnotics Agents: Child & Adolescent Suggested Maximum Formulary Doses
Attachment B – New Drug Applications

1. Lisdexamfetamine (Vyvanse®)
2. Dexmethylphenidate extended release (Focalin ® XR)
3. Methylphenidate extended release capsules (Metadate ® CD)
4. Ramelteon (Rozerem®)

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

Sedative Hypnotics Agents: Child & Adolescent Suggested Maximum Formulary Doses
Modified based on 6/22/07 EFC meeting

Drug	Suggested Maximum Dose (mg/day)			
	Under 65 years (mg/day)	**Over 65 years (mg/day)**	**6-12 years (mg/day)**	**13-17 years (mg/day)**
Amobarbital (Amytal)- **RESERVE USE**	500	500	NR	NR
Chloral Hydrate (Noctec)	1500	1500	*50mg/kg up to max of 1000	*1000
DiphenhydrAMINE (Benadryl)	300	300	1mg/kg up to max of 50	50 mg per dose up to a max 300 mg/day
HydrOXYzine (Atarax, Vistaril)	300	300	2mg/kg up to max of 100	100 mg per dose, max is 100 mg/day
Temazepam (Restoril)	30	15	ND	ND
Trazodone (Desyrel)	200	150	100	200
Triazolam (Halcion)	0.25	0.125	ND	ND
Zaleplon (Sonata)	10	5	NR	NR
Zolpidem (Ambien)	10	5	NR	NR

* for pre-procedure sedation only
NR= Not Recommended
ND= No Maximum Dose Established

Amobarbital[1]
Efficacy: Barbiturates, primarily due to unacceptable adverse effects, are not recommended in the pediatric population.

Recommendation: No maximum dose; use not recommended in children or adolescents.

Chloral Hydrate[1-3]
Efficacy: Most of the pediatric literature regarding chloral hydrate is for pre-procedure sedation induction rather than insomnia. Several controlled clinical trials were available evaluating the use of chloral hydrate for pre-procedure sedation. A PubMed search found no controlled clinical trials evaluating the use of chloral hydrate for insomnia in pediatric patients. Chloral hydrate has a foul odor, potential cardiac effects, and post-sedation "hangover' effects that limit its usefulness for treating insomnia in children. Overall, the maximum recommended dose is 50mg/kg/day or 1gram per day for children and 1gram per day for adolescents when used for pre-procedure sedation.

Recommendation: Maximum dose 50mg/kg/day up to a maximum of 1 gram per day for children, and 1 gram per day for adolescents for pre-procedure sedation. Use of chloral hydrate for insomnia is not recommended.

Diphenhydramine[2-4]

Efficacy: Antihistamines have sedative properties and are commonly prescribed for the treatment of insomnia in children. A recent survey of community-based pediatricians reported antihistamines to be the most commonly recommended nonprescription medication for pediatric insomnia. Although higher maximum doses of diphenhydramine may be used for indications such as allergic rhinitis, allergic reactions, and vertigo (i.e. 150-300mg/day children, 300mg/day adolescents), the recommended maximum dose for insomnia is 1mg/kg or 50mg for children and 50mg for adolescents.

Recommendation: Maximum dose 1mg/kg/day up to a maximum of 50mg per day in children and maximum of 50mg per day in adolescents for insomnia. Higher maximum doses may be allowed for other indications (i.e. severe allergic reactions).

Hydroxyzine[2-5]

Efficacy: Antihistamines have sedative properties and are commonly prescribed for the treatment of insomnia in children. A recent survey of community-based pediatricians reported antihistamines to be the most commonly recommended nonprescription medication for pediatric insomnia. Although antihistamines including hydroxyzine are commonly prescribed for the treatment of insomnia, limited data is available regarding the use of hydroxyzine for this indication. Several controlled clinical trials are available demonstrating hydroxyzine's efficacy for pre-procedure sedation with variable dosing, typically in combination with other sedative agents such as midazolam, meperidine, and chloral hydrate. One study noted high rates of oxygen desaturations and deep sedation with the combination of hydroxyzine with chloral hydrate. According to the Drug Information Handbook the recommended oral dose for preoperative sedation induction in children is 0.6mg/kg/dose for oral hydroxyzine and 0.5-1 mg/kg/dose for intramuscular hydroxyzine. Clinical pharmacology lists the maximum dosage limit as 100mg/day for adolescents and 2mg/kg/day or 100mg/day for children.

Recommendation: Maximum oral hydroxyzine dose 2mg/kg/day up to max of 100mg for children and 100mg per day for adolescents.

Temazepam[1-4,6-7]

Efficacy: In a survey of community based pediatricians, 11.9% reported prescribing at least 1 prescription for benzodiazepines for pediatric insomnia in the last 6 months. Although benzodiazepines are used for pediatric insomnia they can result in residual daytime sedation, impairment in psychomotor performance, disinhibition, nausea and vomiting. With long-term use of benzodiazepines tolerance to the sedative effects may develop. A PubMed search found no controlled trials utilizing temazepam as an agent for insomnia in children or adolescents. Limited information was available regarding the use of temazepam for pre-procedure sedation. One study by Thomas et al. compared temazepam elixir to trimeprazine as premedication in children undergoing tonsillectomy and associated procedures. The study results reported temazepam elixir to be associated with significantly more ectopic beats, postoperative vomiting, and postoperative restlessness. A more recent study by Woodthrope C et al. reports the use of temazepam 1mg/kg in children over 15kg prior to an MRI; limited data regarding safety and efficacy was reported in this study. Due to the lack of information available on treating children and adolescents with temazepam, a maximum suggested dose cannot be established.

Recommendation: No maximum dose established.

Trazodone
Recommendation: 100mg for children, 200mg for adolescents approved at prior DSHS EFC meeting. Consideration should be given to increasing the maximum dose for adults to 200mg.

Triazolam[1-4,8]
Efficacy: In a survey of community based pediatricians, 11.9% reported prescribing at least 1 prescription for benzodiazepines for pediatric insomnia in the last 6 months. Although benzodiazepines are used for pediatric insomnia they can result in residual daytime sedation, impairment in psychomotor performance, disinhibition, nausea and vomiting. With long-term use of benzodiazepines tolerance to the sedative effects may develop. Limited information is available regarding pediatric use of triazolam. A few studies have been conducted looking at use of triazolam as an oral sedative prior to dental procedures. Raadal et al. conducted a randomized, double-blind, clinical trial comparing triazolam 0.03 mg/kg to placebo as a sedative agent in pediatric dentistry. The results showed no significant differences between either group in total time or percent time exhibiting disruptive movements and verbal or non-verbal distress. With the limited information available regarding the use of triazolam in children and adolescents, a maximum suggested dose cannot be established.

Recommendation: No maximum dose established.

Zaleplon[2-3]
Efficacy: No published clinical studies could be found regarding zaleplon use in children and adolescents. The manufacturer was contacted on 6/18/07 and reported no data on file regarding zaleplon use in children and adolescents. Zaleplon has not been studied regarding safety and efficacy in the child and adolescent population so no maximum dose has been established.

Recommendation: Not recommended.

Zolpidem[2-3,9-10]
Efficacy: An 8-week randomized, placebo-controlled study was conducted in 201 pediatric patients aged 6-17 years with insomnia and ADHD. Patients were treated with oral zolpidem 0.25mg/kg/day up to a maximum of 10mg/day (n=136) or placebo (n=65). Zolpidem did not significantly decrease sleep latency to persistent sleep compared to placebo, as measured by polysomnography after 4 weeks of treatment. Psychiatric and nervous system disorders were more frequent with zolpidem versus placebo (23.5% vs. 1.5%). Hallucinations were reported in 7.4% of the pediatric patients receiving zolpidem vs. 0% in placebo. Although no exact percentage is given, it was noted that the incidence of hallucinatory experiences was higher in the age group under 12 years old compared to those over 12 years old. In the pre-marketing adult studies the incidence of hallucinations was less than 1%.

Recommendation: Use in children and adolescents is not recommended.

References:

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June 2007

Lisdexamfetamine dimesylate (Vyvanse®)

Classification: Central Nervous System Stimulant

Pharmacology:

Lisdexamphetamine dimesylate is a pro-drug of dextroamphetamine. After oral administration, lisdexamfetamine dimesylate 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. The mode of therapeutic action in Attention-Deficit/Hyperactivity Disorder (ADHD) is not known. 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*.

Pharmacokinetics:

Absorption: In 18 pediatric patients (6-12 yrs) with ADHD, the Tmax of dextroamphetamine was approximately 3.5 hours following single-dose oral administration of lisdexamfetamine dimesylate either 30mg, 50mg, or 70mg after an 8-hour overnight fast. The Tmax of lisdexamfetamine dimesylate was approximately 1 hour. Food does not affect the observed AUC and Cmax of dextroamphetamine in healthy adults after single-dose oral administration of 70mg of Vyvanse® capsules but prolongs Tmax by approximately 1 hour.

Distribution: Plasma concentrations of unconverted lisdexamfetamine dimesylate are low and transient, generally becoming non-quantifiable by 8 hours after administration.

Metabolism: Lisdexamfetamine dimesylate is converted to d-amphetamine and L-lysine, which is believed to occur by first-pass intestinal and/or hepatic metabolism. Lisdexamfetamine is not metabolized by cytochrome P450 enzymes. *In vitro* studies indicate minor inhibition of CYP2D6 by amphetamine and minor inhibition of CYP1A2, 2D6, and 3A4 by one or more metabolites.

Elimination: After a radiolabeled 70mg oral dose administration, 96% of the oral dose radioactivity was recovered in the urine and only 0.3% recovered in the feces over a 120 hour period. Of the radioactivity recovered in the urine 42% of the dose was related to amphetamine, 25% to hippuric acid, and 2% intact lisdexamfetamine. Elimination half life is less than one hour.

Indications: Indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children aged 6 to 12 years.[1]

Dosage:

In children 6-12 yrs with ADHD who are either starting treatment for the first time or are switching from another medication, 30mg once daily in the morning is the recommended dose. If necessary to increase, dosage may be adjusted in increments of 20mg/day and at approximately weekly intervals. Maximum recommended dose for children is 70mg/day.

Contraindications:

- Patients with symptomatic cardiovascular disease
- Patients with a history of drug abuse
- Patients with advanced arteriosclerosis

- Patients with agitated states; may aggravate symptoms
- Patients with concomitant use of monoamine oxidase inhibitors (MAOI), or within 14 days of MAOI use
- Patients with glaucoma
- Patients with hypersensitivity/idiosyncrasy to sympathomimetic amines
- Patients with hypertension, moderate to severe
- Patients with hyperthyroidism

Precautions:

- Pregnancy Category C
- Patients who use other sympathomimetic drugs
- Patients with Tourette's syndrome and tics
- Long duration of use may lead to dependence
- Patients with a history of amphetamine misuse; may cause sudden death and serious cardiovascular events
- Patients with comorbid bipolar disorder; may precipitate a mixed/manic episode
- Patients with cardiovascular conditions which may be compromised by increases in blood pressure or heart rate (eg, preexisting hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia)
- May cause EEG abnormalities, especially in those with a history of EEG abnormalities; may lower convulsive threshold
- Patients with preexisting psychosis, may exacerbate symptoms of behavior disturbance and thought disorder
- Patients with seizures, especially with a history of; may lower convulsive threshold
- Patients with structural cardiac abnormalities/conditions, serious, especially in children and adolescents; sudden death has been reported with CNS stimulant treatment

Interactions: Similar to other amphetamines

- Coadministration with urinary acidifying agents may lower the blood levels and efficacy of amphetamines
- Effects of adrenergic blockers and anihypertenisives may be inhibited by lisdexamfetamine dimesylate
- Lisdexamfetamine dimesylate may enhance the activity of sympathomimetc agents
- MAO inhibitors slow lisdexamfetamine dimesylate metabolism and potentiate it's effects

Adverse Reactions:

Occurred in at least 5% of the lisdexamfetamine dimesylate patients at a rate twice that of the placebo group: Upper abdominal pain, decreased appetite, dizziness, dry mouth, irritability, insomnia, nausea, vomiting, and decreased weight.

Cost Comparison:

Name	Strength (mg)	Unit Cost
Lisdexamfetamine Dimesylate	30, 50, 70	$ 3.14
Mixed Amphetamine Salts XR	10, 20, 30	$ 3.31
Mixed Amphetamine Salts	5, 10, 20, 30	$ 0.22

Monitoring:

Symptomatic improvement of attention-deficit hyperactivity disorder; blood pressure, pulse, development and growth of pediatric patients; signs and symptoms of cardiac disease, psychosis or mania, seizures, tolerance, and drug dependence

Product Identification:

30mg capsule: white body/orange cap (imprinted NRP104 30mg)
50mg capsule: white body/blue cap (imprinted NRP104 50mg)
70mg capsule: blue body/orange cap (imprinted NRP104 70mg)

Efficacy and Safety:

Two pivotal clinical studies have assessed the efficacy and safety of lisdexamfetamine in the treatment of ADHD. The first trial was a six week, randomized double-blind, placebo- and active-controlled, 3-treatment, 3-periods, crossover study. To be included in the study, subjects had to be treated with a stimulant for at least one month in the previous six months with adequate response. After screening, there was a three week open label dose titration phase to optimal dose with MAS-XR starting with 10 mg daily for the first week. Fifty-two children aged 6-12 years with ADHD received daily morning doses of lisdexamfetamine, mixed amphetamine salts XR (MAS-XR) and placebo, each for one week.

Subjects	Medication groups		
N=10	MAS-XR 10 mg	Lisdexamfetamine 30 mg	Placebo
N=17	MAS-XR 20 mg	Lisdexamfetamine 50 mg	Placebo
N=25	MAS-XR 30 mg	Lisdexamfetamine 70 mg	Placebo

The mean SKAMP Deportment Rating Scale was 0.8 for all active treatments vs. 1.7 for placebo ($p<0.0001$). On the CGI scale, 74%, 72% and 18% of subjects in the lisdexamfetamine, MAS-XR and placebo groups, respectively, were rated as "very much improved" or ""much improved."

Adverse events in >2% of patients reporting				
Adverse Event	Open label MAS-XR (N=52)	Lisdexamfetamine (N=50)	MAS-XR (N=50)	Placebo (N=52)
Any event	24 (46%)	8 (16%)	9 (18%)	8 (15%)
Abdominal Pain	3 (6%)	0 (0%)	0 (0%)	0 (0%)
Upper abdominal pain	3 (6%)	0 (0%)	2 (4%)	1 (2%)
URI	2 (4%)	1 (2%)	1 (2%)	0 (0%)
Decreased appetite	7 (14%)	3 (6%)	2 (4%)	0 (0%)
Headache	8 (15%)	0 (0%)	0 (0%)	0 (0%)
Affect lability	2 (4%)	0 (0%)	0 (0%)	0 (0%)
Insomnia	5 (10%)	4 (8%)	1 (2%)	1 (2%)
Vomiting	1 (2%)	0 (0%)	1 (2%)	2 (4%)
Anorexia	1 (2%)	2 (4%)	0 (0%)	0 (0%)

Diastolic blood pressure was 5 and 3 mmHg higher in those treated with lisdexamfetamine and MAS-XR, respectively, than placebo from 2.5-5 hours post morning dose.[2] Heart rate was 7 and 5 bpm higher in those treated with lisdexamfetamine and MAS-XR, respectively, than placebo from 2.5 hours post morning dose. QTc interval was 6-8 and 5 msec greater in those treated with lisdexamfetamine and MAS-XR, respectively, than placebo from 2 and 10.5 hours post morning dose. Lisdexamfetamine dimesylate and MAS-XR displayed similar efficacy, safety and tolerability in the management of ADHD.

The second trial was a multicenter, randomized, double-blind, forced dose, parallel-group study of 285 children ages 6-12 years.[3] Subjects were excluded from the study if they had any comorbid psychiatric diagnosis. The study consisted of three phases: a one week patient screening, a one week washout period and four weeks of double-blind treatment. Subjects were randomized to four treatment groups, lisdexamfetamine 30 mg, 50 mg, 70 mg (Dosing initiated at 30 mg then increased by 20 mg weekly to target dose) or placebo. Total ADHD-Rating Scale-Version IV score reduction at the end point was 6.2 for the placebo-treated group vs. 21.8, 23.4 and 26.7 for the lisdexamfetamine dimesylate 30 mg, 50 mg and 70 mg groups, respectively (All lisdexamfetamine dimesylate doses $p<0.0001$ vs. placebo). Lisdexamfetamine dimesylate was found to have efficacy and tolerability similar to other extended-release stimulants.

Adverse events reported by ≥2% of all patients:

Body System	Preferred Term	Vyvanse (n=218)	Placebo (n=72)
Gastrointestinal Disorders	Abdominal Pain Upper	12%	6%
	Dry Mouth	5%	0%
	Nausea	6%	3%
	Vomiting	9%	4%
General Disorder and Administration Site Conditions	Pyrexia	2%	1%
Investigations	Weight Decreased	9%	1%
Metabolism and Nutrition	Decreased Appetite	39%	4%
Nervous System Disorders	Dizziness	5%	0%
	Headache	12%	10%
	Somnolence	2%	1%
Psychiatric Disorders	Affect lability	3%	0%
	Initial Insomnia	4%	0%
	Insomnia	19%	3%
	Irritability	10%	0%
	Tic	2%	0%
Skin and Subcutaneous Tissue Disorders	Rash	3%	0%

Conclusions:
Lisdexamfetamine dimesylate has comparable efficacy, safety and cost to MAS-XR and is ~7 times as expensive for daily treatment as MAS. The studies reported use previous responders to treatment and those without comorbid psychiatric illness, which is not representative of the institutions' patient populations. Currently, there are no published studies regarding the abuse potential and thus can not be evaluated. Also, no short-acting version of lisdexamfetamine dimesylate is available.

Recommendations:
Addition to the formulary is not recommended.

References:
[1]Product Information: Vyvanse®, Lisdexamfetamine dimesylate. Shire US Inc, Wayne, PA, 2007

[2]Data on File, Shire, NRP 104-201. A phase 2, randomized, double-blind, placebo- and active-controlled, 3-treatment, 3-period, crossover study with one week per treatment and once-a-day dosing of either NRP104, Adderall XR ® or placebo in children aged 6 to 12 years with attention-deficit hyperactivity disorder (ADHD): Final clinical study report, 2005 July 13.

[3]Biederman J, Krishnan S, Zhang Y, et al. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. *Clin Ther*. 2007;29(3):450-463.

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Attachment B-2

Dexmethlyphenidate Hydrochloride Extended-Release
(Focalin XR®)

Classification: Central Nervous System Stimulant

Pharmacology:

Dexmethylphenidate hydrochloride 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.

Pharmacokinetics:

Absorption: Mean absolute bioavailability of dexmethylphenidate when administered in various formulations is 22-25%. Dexmethylphenidate produces a bi-modal pharmacokinetic profile that displays a peak at approximately 1.5 hours (range 1-4 hours) and a second peak at approximately 6.5 hours (range 4.5-7 hours) after administration. Focalin® XR uses the proprietary SODAS® (Spheroidal Oral Drug Absorption System) technology. Each capsule contains half immediate-release beads and half enteric-coated, delayed-release beads.

Distribution: The plasma protein binding of dexmethylphenidate is not known; however, racemic methylphenidate is 12-15 % bound to plasma proteins. The volume of distribution for dexmethylphenidate is 2.65 ± 1.11 L/kg.

Metabolism: Dexmethylphenidate is primarily metabolized by de-esterification to d-ritalinic acid, which has little to no pharmacologic activity.

Elimination: The elimination half-life of dexmethylphenidate in adults is variable with a mean of 3 hours (typical range 2-4.5 hours). Children tend to have a slightly shorter elimination half-life ranging from 2-3 hours.

Indications:

Indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged 6 years and older[1]

Dosage:

Recommended starting dose for patients not currently taking racemic methylphenidate, dexmethylphenidate, or patients who are on stimulants other than methylphenidate is 5 mg once daily for pediatric patients and 10 mg once daily for adults. Dosage adjustments may be made at weekly intervals in 5 mg increments in pediatric patients and 10 mg increments in adults (maximum recommended dose is 20 mg per day for children as well as adults). Extended release capsule may be opened and beads may be sprinkled on applesauce if necessary.

For patients currently using methylphenidate, the recommended starting dose of dexmethylphenidate XR is one half the total daily dose of racemic methylphenidate. Patients currently taking dexmethylphenidate immediate release can be converted to the extended release by using the same total daily dose of dexmethylphenidate given once daily.

Contraindications:

- Patients with hypersensitivity to methylphenidate, dexmethylphenidate or other ingredients in the product
- Patients with marked anxiety, tension, and/or agitation
- Patients with glaucoma
- Patients with motor tics and those with a family history or diagnosis of Tourette's syndrome
- Patients treated with MAOIs (concurrent or within preceding 14 days)

- Patients with structural cardiac abnormalities, cardiomyopathy, serious arrhythmias, or other serious cardiac problems

Precautions:
- Pregnancy Category C
- Patients with hypertension, heart failure, recent myocardial infarction, coronary artery disease, or other cardiac conditions
- Patients with pre-existing psychosis
- Patients with bipolar disorder
- Patients with a seizure disorder or history of seizures
- Patients with history of drug dependence or alcoholism
- Use in children under 6 years of age

Interactions:
- Coadministration of antacids or acid suppressants may alter the release of dexmethylphenidate because the modified release component is pH dependent
- Dexmethylphenidate should not be used in patients treated with a monoamine oxidase inhibitor (MAOI) currently or within the preceding two weeks due to the risk of hypertensive crisis
- Possible increase in blood pressure with concomitant pressor agents
- Methylphenidate use may decrease the effectiveness of antihypertensives
- Methylphenidate has been reported to inhibit coumarin anticoagulants, anticonvulsants (e.g. phenobarbital, phenytoin, primidone), and tricyclic agents (e.g. imipramine, clomipramine, desipramine).

Adverse Reactions:

Focalin XR® has demonstrated similar bioavailability to the immediate-release formulation and has, therefore, demonstrated a similar CNS-stimulant side-effect profile. The most common reasons for drug discontinuation were motor or vocal tics, anorexia, insomnia, and tachycardia in the child and adolescent clinical trials. Increased blood pressure may also been reported and appears to be dose dependent.

Costs and Monitoring:

Focalin XR® 5mg $2.92, 10mg $2.96, 15mg $3.04, and 20mg $3.04 per capsule, QD dosing

Price Comparison:
Focalin® 5mg $0.73 and 10mg $1.05, BID dosing
Concerta® 18mg $3.10, 27mg $3.18, 36mg $3.28, 54mg $3.57, QD dosing
Methylphenidate 5mg $0.07, 10mg $0.10, 20mg $0.13, BID-TID dosing

Schedule CII
In patients with cardiac disease or findings suggesting cardiac disease an EKG is recommended. Height and weight in children and adolescents. Periodic CBC with differential and platelet count is recommended during prolonged therapy.

Product Identification:

Capsule (extended release):
5 mg light blue, imprinted NVR D5
10 mg light caramel, imprinted NVR D10
15 mg green, imprinted NVR D15
20 mg white, imprinted NVR D20

Efficacy:

The efficacy of Focalin XR® for the treatment of ADHD was demonstrated in randomized, placebo-controlled studies in children and adolescents as well as adults. The first study randomized 54 children 6-12 years of age, stabilized on methylphenidate 20-40mg per day.[2] Patients received 5 days of treatment with Focalin XR® 20mg/day or placebo after a 1 day wash-out. Evaluations occurred before medication administration and 1, 2, 4, 6, 8, 10, 11, and 12 hours after medication administration. In the primary efficacy measure, Focalin XR® 20mg per day group showed significant improvement over placebo as early as the 1 hour postdose SKAMP-Combined score ($p<0.001$). Significant improvement in the SKAMP-Combined score was maintained 12 hours after medication administration.

A second study included 97 children and adolescents 6-17 years of age.[3] Patients were randomized to Focalin XR® (up to 30mg per day) or placebo for 7 weeks. The primary efficacy measure, Conners ADHD Scale-Teacher version (CADS-T) total subscale score from baseline to final rating significantly improved with Focalin XR® compared with placebo ($p<0.001$).

The efficacy of Focalin XR® for the treatment of ADHD in 221 adults (ages 18-60) was demonstrated in a 5-week randomized, double-blind, placebo-controlled study.[4] Patients were randomized to receive a fixed dose of 20mg, 30mg, or 40mg of Focalin XR® or placebo once daily (initiated at 10mg per day and titrated at 10mg per week increments). All three doses of Focalin XR® were significantly better than placebo with no obvious increase in efficacy with increasing dose.

To date, safety and efficacy comparisons between Focalin XR® and methylphenidate (Ritalin) have not been conducted. Dexmethylphenidate and methylphenidate have been studied vs. placebo; however, the study was not designed to compare efficacy between the two active components.[5] Patients in this study received dexmethylphenidate, methylphenidate, or placebo for 4 weeks. The primary efficacy variable was change from baseline to the final study visit in the Teacher Swanson, Nolan, and Pelham (SNAP) rating scale. Both treatment groups showed significant improvement in scores and the effect size was large for both active agents (effect size=1.0 for both). Parent SNAP ratings and Math Tests showed significant improvement at 3pm with both agents; whereas, only the dexmethylphenidate showed significant improvement at 6pm. Both the dexmethylphenidate and methylphenidate groups had significantly higher responder rates based on CG-I scores than placebo.

Conclusions:

Currently, only pharmacokinetic comparisons with methylphenidate have been conducted for Focalin XR®. Studies are not available to conclude if Focalin XR® provides a superior drug profile in regard to safety, tolerability and efficacy with any formulation of methylphenidate. One study comparing Focalin® to methylphenidate suggests similar efficacy and safety, and perhaps longer duration of action during the afternoon than methylphenidate with twice daily dosing of both agents.[5] Methylphenidate may be administered three times a day, but this dosing schedule was not studied in the trial. Focalin XR® is comparable in price to Concerta®, which is currently available on the formulary and is also administered once daily. Focalin XR® is $0.94 to $1.91 more expensive per day than

Focalin® for daily doses of 20mg and 10mg respectively. Focalin XR® is $2.78 to $2.83 (11-22x) more expensive per day than equivalent doses of generic methylphenidate 40mg and 20mg respectively.

Recommendation:

Not recommended for addition to the formulary.

References:

1. Product Information: FOCALIN(TM) XR extended-release oral capsules, dexmethylphenidate hydrochloride extended-release oral capsules. Novartis Pharmaceuticals Corporation, East Hanover, NJ, 2006.
2. Silva RR, Muniz R, Pestreich L, Childress A, Brams M, Lopez FA, Wang J. Efficacy and duration of effect of extended-release dexmethylphenidate versus placebo in schoolchildren with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology* 2006;16(3):239-251.
3. Greenhill L, Muniz R, Ball, RR, Levine A, Pestreich L, and Jiang H. Efficacy and safety of dexmethylphenidate extended-release capsules in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2006;45(7):817-823.
4. Spencer TJ, Adler LA, McGough JJ, Muniz R, Jiang J, Pestreich L, and the adult ADHD research group. Efficacy and safety of dexmethylphenidate extended-release capsules in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2007;61:1380-1387.
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June 2007

Methylphenidate Hydrochloride Extended-Release Capsules (Metadate CD®)

Classification: Central Nervous System Stimulant

Pharmacology:

Methylphenidate 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. Methylphenidate is a racemic mixture, the *d-threo* enantiomer is more pharmacologically active than the *l-threo* enantiomer. The extended-release capsules comprise both immediate-release (IR), 30%, and extended-release (ER), 70%, beads.

Pharmacokinetics:

Absorption: Methylphenidate is readily absorbed. Metadate CD® has a plasma/time concentration profile showing two phases of drug release: The initial slope of Metadate CD® is similar to a methylphenidate immediate-release tablet, occurring 1.5 hours after dose intake and a second peak occurs approximately 4.5 hours after dose intake, followed by a gradual decline.

Distribution: Racemic methylphenidate is 12-15 % bound to plasma proteins.

Metabolism: Methylphenidate is metabolized via deesterification to alpha-phenylpiperidine acetic acid (ritalinic acid). The metabolite has little or no pharmacologic activity. *In vitro* studies showed that methylphenidate was not metabolized by cytochrome P450 isoenzymes, and did not inhibit cytochrome P450 isoenzymes at clinically observed plasma drug concentrations.

Elimination: In healthy adult volunteers, the mean terminal half-life ($t_{1/2}$) of methylphenidate following administration of Metadate CD® ($t_{1/2}$=6.8h) is longer than the mean terminal ($t_{1/2}$) following administration of methylphenidate HCl immediate-release tablets ($t_{1/2}$=2.9) and methylphenidate HCl sustained-release tablets ($t_{1/2}$=3.4h). These observations suggest that the elimination process for Metadate CD® is controlled by the release rate of methylphenidate from the extended-release formulation, and that the drug-absorption is the rate-limiting process.

Indications:

Indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged 6 years and older.[1]

Dosage:

Metadate CD® is administered once daily in the morning, before breakfast. Metadate CD® may be swallowed whole with the aid of liquids or the capsule may be opened and the capsule contents sprinkled onto a small amount of applesauce and given immediately.

Initial dose of Metadate CD® is 20 mg once daily. Dosage may be adjusted in weekly 10-20 mg increments to a maximum of 60 mg/day taken once daily in the morning.

Contraindications:

- Patients with hypersensitivity to methylphenidate, dexmethylphenidate or other ingredients in the product
- Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency should not take this medicine as the product contains sucrose.
- Patients with marked anxiety, tension, and/or agitation

- Patients with glaucoma
- Patients with motor tics and those with a family history or diagnosis of Tourette's syndrome
- Patients treated with MAOIs (concurrent or within preceding 14 days)
- Patients with structural cardiac abnormalities, cardiomyopathy, serious arrhythmias, severe hypertension, angina pectoris, heart failure, recent myocardial infarction, hyperthyroidism/throtoxicosis or other serious cardiac problems.
- Patients given halogenated anesthetics due to risk of sudden increase in blood pressure during surgery. If surgery is planned, Metadate CD® should not be taken on the day of surgery.

Precautions:
- Pregnancy Category C
- Patients with hypertension, heart failure, recent myocardial infarction, coronary artery disease, or other cardiac conditions
- Patients with pre-existing psychosis
- Patients with bipolar disorder
- Patients with a seizure disorder or history of seizures
- Patients with history of drug dependence or alcoholism
- Use in children under 6 years of age

Interactions:
- Clearance of methylphenidate might be affected by urinary pH, either being increased with acidifying agents or decreased with alkalizing agents.
- Dexmethylphenidate should not be used in patients treated with a monoamine oxidase inhibitor (MAOI) currently or within the preceding two weeks due to the risk of hypertensive crisis
- Possible increase in blood pressure with concomitant pressor agents
- Methylphenidate use may decrease the effectiveness of antihypertensives
- Methylphenidate has been reported to inhibit coumarin anticoagulants, anticonvulsants (e.g. phenobarbital, phenytoin, primidone), phenylbutazone and some antidepressant agents (e.g. TCAs and SSRIs).
- Serious adverse events have been reported in concomitant use with clonidine although no causality for the combination has been established. Using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.
- Risk of sudden blood pressure increase during surgery with halogenated anesthetics. Metadate CD® should not be taken on the day of the surgery.

Adverse Reactions:

During the controlled clinical trials there were two drug discontinuations due to adverse events including rash and pruritus in one patient and headache, abdominal pain, and dizziness in another patient. Treatment-emergent events that occurred in 5% or more of patients treated with Metadate CD® include: headache 12% (placebo 8%), abdominal pain 7% (placebo 4%), anorexia 9% (placebo 2%), and insomnia 5% (placebo 2%).

Costs and Monitoring:

Metadate CD® 10mg, 20mg and 30mg $2.30 per capsule, 40mg $3.15 per capsule, and 50mg and 60mg $4.21 per capsule; QD dosing

Price Comparison:
Concerta® 18mg $3.10, 27mg $3.18, 36mg $3.28, 54mg $3.57, QD dosing
Methylphenidate 5mg $0.07, 10mg $0.10, 20mg $0.13, BID-TID dosing
Schedule CII
In patients with cardiac disease or findings suggesting cardiac disease an EKG is

recommended. Height and weight in children and adolescents. Periodic CBC with differential and platelet count is recommended during prolonged therapy.

Product Identification:

- 10 mg green/white capsule, imprinted with "UCB 579" in white letters on the white cap and "10 mg " in black letters on the white body of the capsule
- 20 mg blue/white capsule, imprinted with "UCB 580" in white letters on the blue cap and "20 mg " in black letters on the white body of the capsule
- 30 mg reddish-brown/white capsule, imprinted with "UCB 581" in white letters on the reddish-brown cap and "30 mg " in black letters on the white body of the capsule
- 40 mg yellow ivory/white capsule, imprinted with "UCB 582" in white letters on the yellow ivory cap and "40 mg " in black letters on the white body of the capsule
- 50 mg purple/white capsule, imprinted with "UCB 583" in white letters on the purple cap and "50 mg " in black letters on the white body of the capsule
- 60 mg white/white capsules, imprinted with "UCB 584" in black letters on the white cap and "60mg" in black letters on the white body of the capsule

Efficacy:

Metadate CD® (MCD) was evaluated in a 3 week double-blind, parallel, placebo-controlled trial in 321 children 6-16 years of age with ADHD.[2] Subjects randomized to MCD were initiated on 20mg once daily and titrated up to a maximum of 60mg per day. The primary outcome measure was a reduction in ADHD symptom severity using the 10-item Conners' Global Index teacher version. The mean age of the participants was 9 years and the MCD mean dose at study endpoint was 40.7mg per day (1.28 mg/kg/day). MCD significantly improved ADHD symptoms ratings vs. placebo on the primary outcome measure as well as many secondary efficacy measures. The only side effect significantly greater for MCD vs. placebo was anorexia.

Metadate CD® (MCD), Concerta® (CON), and placebo were compared in a double-blind, double-dummy, 3-way crossover study.[3] Eligible patients were assigned to a dose level according to their preexisting dosing requirement for MPH and remained at this level for the study duration (MCD 20, CON 18 or Placebo; MCD 40, CON 36, or Placebo; MCD 60, CON 54, or Placebo). Each of the 3 treatments was administered for 7 days without an intervening washout period. On the 7th day of each treatment week children attended a laboratory school where assessments for response, assessments for adverse events, and patient and parent side effect reports were obtained. The 3 primary outcome measures were the Swanson, Kotkin, Atkins, M/Flynn, Pelham Scale (SKAMP) consisting of 6 deportment items and 7 attention items as well as the Permanent Product (PERMP) math test. Outcome assessments were conducted at 1.5, 3, 4.5, 6, 7.5, and 12 hours after dose. Results indicated that MCD>CON>Placebo during the morning hours, MCD=CON>Placebo during the afternoon and CON>MCD=Placebo in the early evening. Overall, MCD showed superior reduction in ADHD symptoms during the early morning hours and CON showed superior reduction in ADHD in the early evening. Both active treatments appeared to be equivalent and superior in efficacy to placebo in efficacy during the afternoon. There were no significant differences among the 3 treatments with regard to adverse events, side effect ratings, or vital signs.

A second randomized, double-blind, three-arm, parallel-group efficacy study compared Equasym™ XL (marketed as Metadate CD® in the US), immediate release methylphenidate (dosed twice daily), and placebo.[4] Subjects included in the study were 6-12 years of age with one of the three subtypes of ADHD per DSM-IV on a stable dose of methylphenidate for at least 3 weeks prior to screening. The primary efficacy measure was the difference between active treatments in the inattention/overactivity component of the overall Teacher's IOWA Conners' Questionnaire during the final week of treatment (week 3). A total of 318

patients received at least one dose of study medication. Equasym™ XL was non-inferior to methylphenidate immediate release given twice-daily and both methylphenidate treatment groups experienced significant improvement compared to placebo ($p < 0.001$).

Conclusions:

Based on the available published literature, Metadate CD® appears to be an efficacious and relatively safe medication for the treatment of ADHD with the convenience of once daily dosing. Metadate CD® is available in a capsule formulation consisting of IR and ER beads in which the contents can be sprinkled on applesauce and consumed. The current formulary biphasic methylphenidate product, Concerta®, is available in an osmotic tablet formulation. The two biphasic once daily products are similar in cost with Metadate CD® being slightly less expensive at the lower end of the dosage range and Concerta® being slightly more expensive at the upper end of the dosage range. One study indicates that although Metadate CD® and Concerta® are effective for the treatment of ADHD, Metadate CD® may have superior efficacy in the early morning hours and Concerta® may be more effective in the early evening.[3] One non-inferiority study did not find Equasym™ XL (marketed as Metadate CD® in the US) to be inferior to immediate release methylphenidate dosed twice a day and both methylphenidate products were superior to placebo. A 40mg dose of Metadate CD® is 12x more expensive than the equivalent daily dose of immediate release methylphenidate.

Recommendation:

Addition to the formulary is recommended.

References:

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Ramelteon
(Rozerem™)

Classification: Hypnotic Agent

Pharmacology:

Ramelteon is a melatonin receptor agonist which selectively binds melatonin MT_1 and MT_2 receptors in the suprachiasmatic nucleus of the hypothalamus, with little affinity for the MT_3 receptor. Activation of MT_1 and MT_2 receptors by endogenous melatonin is believed to be involved in generation of the circadian rhythm underlying the normal sleep-wake cycle. The MT_1 receptor is believed to be involved in producing sleepiness, while the MT_2 receptor is thought to be involved in phase-shifting effects on the circadian rhythm. Ramelteon has a greater affinity and selectivity for MT_1 receptors compared with melatonin, which would theoretically offer an advantage over melatonin in the treatment of sleep-onset insomnia.[1,2]

Pharmacokinetics:

Absorption: Absorption is rapid after oral administration, with a median time to peak concentration (T_{max}) ranging from 0.5 to 1.5 hours. While total absorption is at least 84%, the absolute bioavailabilty is low (1.8%) due to extensive first-pass metabolism.

Distribution: Ramelteon is approximately 82% protein-bound, primarily to albumin. Mean volume of distribution after IV administration is 73.6 L, suggesting substantial tissue distribution.

Metabolism: Hepatic metabolism takes place largely through CYP1A2, with minor involvement of CYP3A4 and CYP2C9/19. Ramelteon has 4 principal metabolites, with M-II being the most prevalent. M-II has some affinity for MT_1 and MT_2 receptors, but is less potent than the parent drug. Other known metabolites are inactive. Mean systemic exposure is 20- to 100-fold higher for M-II compared with ramelteon.

Elimination: Elimination is rapid, with an elimination half-life ranging from 1 to 2.6 hours. Approximately 84% of the dose is excreted in the urine, with 4% eliminated through the feces. Less than 0.1% of the dose is excreted unchanged. The half-life of M-II is 2-5 hours.

Indications:

Ramelteon is indicated for the treatment of insomnia characterized by difficulty with sleep onset.

Dosage and Administration:

The recommended dose is 8 mg taken within 30 minutes of going to bed. Administration of ramelteon with or immediately after a high-fat meal is not recommended, as this has been shown to substantially delay $T_{max.}$

Contraindications:

- Hypersensitivity to ramelteon or any component of the formulation

Precautions:

- Avoid use in patients with severe hepatic impairment; use caution in patients with moderate hepatic impairment
- Avoid use in combination with fluvoxamine
- Not recommended for patients with severe OSA or COPD
- Avoid use of alcohol in combination
- Avoid driving/operating heavy machinery following administration

- Activities following administration should be limited to those necessary to prepare for bed
- Worsening of depression or suicidal thoughts may occur in depressed patients
- Decreased testosterone levels and increased prolactin levels have been associated with use in adults
- Pregnancy Category C

Interactions:

Co-administration of fluvoxamine, a strong CYP1A2 inhibitor, substantially increases ramelteon AUC and C_{max}. Ramelteon should not be used in combination with fluvoxamine, and caution is advised when using ramelteon in combination with other CYP1A2 inhibitors (e.g. amiodarone, ciprofloxacin).[1,2] Caution is also advised in subjects taking strong CYP3A4 inhibitors (e.g. ketoconazole) and strong CYP2C9 inhibitors (e.g. fluconazole), as exposure to ramelteon and M-II is increased with concomitant use. Efficacy of ramelteon may be reduced when used in combination with strong CYP inducers, such as rifampin.

Adverse Reactions:

In pre-marketing clinical trials of ramelteon, 6% of patients receiving ramelteon discontinued treatment secondary to an adverse event compared with 2% of those receiving placebo. The most frequent adverse events leading to study discontinuation in patients receiving ramelteon were somnolence (0.8%), dizziness (0.5%), nausea (0.3%), fatigue (0.3%), headache (0.3%), and insomnia (0.3%). Ramelteon does not appear to be associated with any next-day residual effects, or with rebound insomnia after abrupt discontinuation.

Cost Comparison of Sedative-Hypnotic Agents:

Generic Name	Brand Name	Strength	AWP Cost (per tablet)	Net Cost (per tablet)
Temazepam*	Restoril	15 mg	$0.71	$0.10
Triazolam*	Halcion	0.125 mg	$0.64	$0.19
Lorazepam	Ativan	1 mg	$0.91	$0.17
Clonazepam	Klonopin	1 mg	$0.91	$0.08
Trazodone	Desyrel	100 mg	$0.78	$0.07
Diphenhydramine	Benadryl	50 mg	$0.13	$0.04
Zolpidem*	Ambien	10 mg	$4.62	$0.07
Eszopiclone*	Lunesta	2 mg	$4.40	$3.41
Zaleplon*	Sonata	10 mg	$3.90	$3.02
Ramelteon*	Rozerem	8 mg	$3.36	$2.58

* FDA-approved for the treatment of insomnia
- Shaded rows indicate non-formulary items

Monitoring:

No standard monitoring is required. Prolactin and testosterone levels may be appropriate for patients presenting with unexplained amenorrhea, galactorrhea, decreased libido, or problems with fertility.

Product Identification:

Round, pale orange-yellow, film-coated, 8 mg tablets; “TAK” and RAM-8” printed on one side

Efficacy:

A multicenter, randomized, double-blind, placebo-controlled, five-period crossover study was undertaken to evaluate the efficacy, safety, and dose-response of ramelteon in patients with

chronic insomnia. A total of 107 adult patients were randomized to a dosing sequence that included 4, 8, 16, and 32 mg of ramelteon and placebo. Patients received a single dose of each treatment, with a 5- to 12-day washout period between treatments. Polysomnography (PSG) was conducted on each night of treatment administration. All doses of ramelteon resulted in statistically significant reductions in mean latency to persistent sleep based on PSG recordings. The reduction in mean sleep latency with ramelteon compared to placebo ranged from 13.4 to 14.8 minutes. Mean total sleep time recorded by PSG was also significantly improved with each dose of ramelteon, though subjective improvements in total sleep time were no different than placebo. Increases in mean PSG-recorded total sleep time ranged from 10.7 to 17.9 minutes.[3]

Another study evaluated the effects of ramelteon in 405 adult patients with chronic insomnia using a double-blind, placebo controlled design. Patients received ramelteon 8 mg, ramelteon 16 mg, or placebo for 35 nights. PSG was conducted on the first two nights of weeks 1, 3, and 5 of treatment. Based on PSG results, both doses of ramelteon significantly reduced the average latency to persistent sleep at the evaluated time points when compared to placebo. The reduction in mean sleep latency at 5 weeks compared to placebo was 11.0 minutes for ramelteon 8 mg and 13.0 minutes for ramelteon 16 mg. No statistically significant improvements in mean PSG-recorded total sleep time were found at study endpoint.[1,4]

The efficacy and safety of ramelteon in 829 outpatients aged 65 years and older with chronic insomnia was evaluated in a randomized, double-blind, parallel-group study. Patients were randomized to receive ramelteon 4 mg, ramelteon 8 mg, or placebo for 35 nights. Efficacy was assessed through patient-recorded sleep diaries. A significant difference in patient-reported sleep latency was seen with both doses of ramelteon compared to placebo. The reduction in mean sleep latency compared to placebo at the 5-week endpoint was 7.2 minutes for ramelteon 4 mg and 12.9 minutes for ramelteon 8 mg. There were no statistically significant differences in patient-reported total sleep time for either dose of ramelteon at study endpoint.[5] A similarly designed study performed in younger adults (aged 18-64 years) using ramelteon doses of 8 mg and 16 mg did not find a similar reduction in patient-reported sleep latency compared to placebo.[1]

A multicenter, three-period, crossover trial also evaluated the efficacy and safety of ramelteon in 100 patients aged 65 years and older with a history of chronic insomnia. Ramelteon 4 mg, ramelteon 8 mg, and placebo were administered for two consecutive nights in three separate treatment phases. PSG was used to measure sleep parameters. Both doses of ramelteon reduced PSG-recorded latency to persistent sleep compared to placebo, with a reduction in mean sleep latency of 9.7 minutes for ramelteon 4 mg and 7.6 minutes for ramelteon 8mg. A statistically significant increase in PSG-recorded total sleep time was reported, though subjective improvements in total sleep time were not found.[6]

The effects of ramelteon on 375 healthy adult volunteers were studied in a randomized, double-blind, placebo-controlled trial. The authors considered the study procedures to represent a model of transient insomnia, as subjects were required to stay overnight at a sleep laboratory for PSG recordings and would theoretically have disturbed sleep brought about by sleeping in a novel environment. Patients were randomized to receive a single administration of ramelteon 16 mg, ramelteon 64 mg, or placebo prior to bedtime at the sleep laboratory. Both doses of ramelteon produced a statistically significant reduction in mean PSG-recorded latency to persistent sleep as compared to placebo. Mean sleep latency was reduced by 10.5 minutes for ramelteon 16 mg and 9.1 minutes for ramelteon 64 mg. Mean increases in total sleep time of 14.1 minutes for ramelteon 16 mg and 11.1 minutes for ramelteon 64 mg were found to be statistically significant.[7]

To date, no published studies have evaluated the efficacy of ramelteon compared to other sedative-hypnotic agents for the treatment of insomnia. Although the greater selectivity and

affinity of ramelteon for the MT1 receptor theoretically offers an advantage over melatonin in induction of sleep, this has not been proven in clinical trials.

Abuse and Dependence:
Ramelteon is not a controlled substance. An 18-day, double-blind crossover study was conducted to evaluate the abuse potential and impairing effects of supratherapeutic doses of ramelteon compared with triazolam. The study enrolled 14 adult patients with a current or past DSM-IV diagnosis of substance abuse or dependence who also reported nonmedical use of a sedative drug in the past year. Each patient received ramelteon 16 mg, ramelteon 80 mg, ramelteon 160 mg, triazolam 0.25 mg, triazolam 0.5 mg, triazolam 0.75 mg, and placebo in seven separate experimental sessions. Triazolam was associated with significant, dose-related effects on patient-reported drug strength and drug liking compared with placebo, though ramelteon did not differ from placebo on these measures. Significant, dose-related impairment in cognitive and motor performance was also seen with triazolam, but not ramelteon. When asked to guess the identity of the study medication given, 11 of the 14 patients identified the highest dose of ramelteon (160 mg) as placebo, while only 2 of 14 patients identified the highest dose of triazolam (0.75 mg) as placebo.[8]

Conclusions:
Ramelteon produces its hypnotic effect through a novel mechanism of action (agonism of melatonin receptors), and does not appear to have the concerning abuse potential associated with some other sedative-hypnotics. In fact, ramelteon is the only FDA-approved prescription medication for the treatment of insomnia that is not a controlled substance. The primary advantages of ramelteon appear to be its lack of abuse potential and safety profile. Despite these advantages, the cost-effectiveness of using ramelteon for the treatment of insomnia is unclear. Head-to-head clinical trials are required to determine the relative effectiveness of ramelteon compared to other available sedative-hypnotic agents. Decreases in sleep latency with ramelteon compared to placebo in clinical trials were small, ranging from 7.6 to 13.4 minutes for ramelteon 8 mg. In addition to the seemingly small treatment effect, ramelteon is much more expensive than other commonly used treatments for insomnia. The net cost difference between one dose of ramelteon 8 mg and zolpidem 10 mg or trazodone 100 mg is $2.51.

Recommendation:
Not recommended for addition to the formulary.

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