CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-259

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

APPLICATION INFORMATION

NDA: 21-259
SPONSOR: Medeva Americas, Inc.
Date submitted: March 31, 2000
Date Received: April 3, 2000
User Fee Due Date: February 3, 2001

DRUG NAME

Generic Name: methylphenidate hydrochloride modified-release capsules
Proposed Trade Name: Metadate ™ MR Capsules

DRUG CATEGORIZATION

Pharmacological Class: Psychostimulant
Proposed Indication: Attention Deficit Disorder
Dosage Forms: 20 mg capsule (IR:ER=30:70)
Route: Oral

REVIEWER INFORMATION

Medical Officer: Roberta L. Glass, M.D.
Review Completion Date: December 7, 2000

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PLEASE NOTE: For the purposes of this review (and to be consistent with the sponsor's terminology in the submitted NDA) the following abbreviations are used:

MPH-IR =methylphenidate-immediate release.
MPH-ER =methylphenidate-extended release.
MPH-SR = methylphenidate-sustained release.
MPH-MR =methylphenidate-modified release: the study drug (this name may change once the sponsor and FDA agree on a trade name).

1.0 Material Utilized in Review

Original NDA Submission: April 3, 2000.
Addendum Submissions: September 16, 2000; July 7, 2000; June 9, 2000.
Consultation from OPDRA regarding proposed proprietary name (6/27/00).
Statistical Review by Kallapa Koti, Ph.D. (draft).

2.0 Background

2.1 Indication

Psychostimulants have been used with increasing frequency in the treatment of Attention Deficit/Hyperactivity Disorders (ADHD) over the past thirty years. Various formulations have been marketed for the indication of ADHD using the following three basic compounds: methylphenidate (e.g. Ritalin, Ritalin SR, Metadate ER, Concerta), dextroamphetamine (e.g. Dexedrine, Adderall), and pemoline (Cylert). Pemoline is a category IV controlled substance, while the methylphenidate and the dextroamphetamine derivatives are a category II controlled substance.

Because methylphenidate immediate release requires dosing during the school day, there has been a need for an effective once-a-day dosing treatment that would provide sustained symptomatic relief for children suffering with ADHD throughout the day. Although there has been one formulation (Ritalin Sustained Release) with a once-a-day dosing regimen, this formulation apparently has not been as success a treatment as multiple dosing of the immediate release.

Therefore, the rationale of this drug product is to provide a once daily dosing which would provide a therapeutic effect of increased concentration and lessened hyperactivity through out the day, eliminating the need for a midday dosing.

2.2 Important Information from Related INDs and NDAs and from Pharmacologically Related Agents

The IND for this product is 52,318. Other related INDs and NDAs are the following:

Concerta (NDA 20-121; Alza)
Ritalin (NDA 10-187 Novartis)
Ritalin SR (NDA 18-029 Novartis)

[ ]

2.3 Administrative History

The sponsor submitted the original IND to FDA on November 8, 1996. A proposal to include a single adequate and well controlled clinical study in children with ADHD to support labeling claims was submitted by the sponsor, and was agreed to in a DNDP correspondence of June 25, 1998.

In an amendment (submitted October 9, 1998) of the pivotal study, MAI 1001-04, the sponsor proposed changing the procedure of statistical analysis to utilize an "adaptive randomization scheme." In the DNDP letter of March 25, 1999, it was communicated to the sponsor that they had not provided adequate justification to use this alternative statistical scheme, and it was recommended that the sponsor return to the plan of utilizing a conventional stratified randomization. The sponsor amended this protocol again (submitted May 13, 1999) to re-adopt the conventional stratified randomization.

A pre-NDA meeting was held with the sponsor on December 9, 1999 during which time many issues regarding clarification and recommendations for the biopharmaceutical studies were discussed. At this meeting, the sponsor was advised to include pharmacokinetic data on the 60 mg strength dosing be submitted with the NDA. The sponsor has filed this application as a 505(b)(2).

2.4 Proposed Directions for Use

The sponsor has listed the indications as Attention Deficit Hyperactivity Disorders and Narcolepsy. [It is noted that the sponsor has not submitted any efficacy data for the indication of Narcolepsy.]

The recommended starting dose is 20 mg, which would include 6 mg MPH-IR and 14 mg of MPH-ER. Dosing is to be administered in the morning before breakfast. Based on the degree of efficacy observed and tolerability, it is recommended that dosing be increased weekly in increments of 20 mg up to a maximum of 60 mg/day.

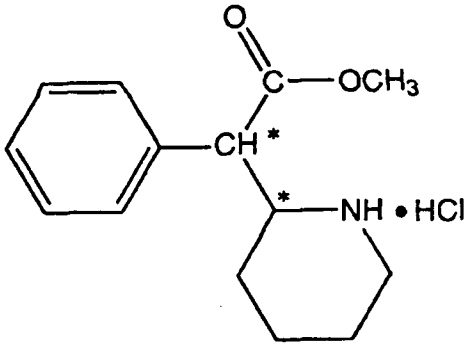
2.5 Foreign Marketing

Methylphenidate hydrochloride modified-release capsules is not marketed anywhere in the world.

The sponsor of this NDA, Medeva, has an immediate release formulation of methylphenidate hydrochloride (Equasym ™) that was approved for marketing on February 22, 2000 in the United Kingdom. The immediate-release formulation of methylphenidate hydrochloride is marketed by companies other than the sponsor in the following countries: Belgium, Canada, Denmark, France, Germany, Greece, Ireland, Netherlands, Norway, Philippines, Spain, Taiwan, and United Kingdom.

3.0 Chemistry

The chemical structure for methylphenidate is the following:



The chemical name is α-phenyl-2-piperidineacetatic acid methyl ester hydrochloride. The study drug contains the enantiomeric forms of both the *d-threo* and the *l-threo* isomers of methylphenidate hydrochloride.

The composition of each 20 mg capsules contains both an immediate-release (IR) and an extended-release (ER) component. Each 20 mg capsules contains 30 % (6 mg) of IR beads, and 70% (14 mg) of ER beads.

The sponsor has proposed the trade name of ' However, a consult obtained from OPDRA recommended that another name be chosen, because of potential confusion with marketed trade name products (see consult of 6/27/00). The sponsor and FDA are currently exploring alternative trade names. Also of note is that the sponsor currently has marketed a product named Metadate-ER.

4.0 Animal Pharmacology and Toxicology

Although not specifically conducted to su pport this NDA, new animal reproductive and toxicity studies were submitted with this NDA. Reproductive and developmental toxicity studies showed marginally lower fetal weight at doses showing maternal toxicity & lower weight gain, increased total litter loss, decreased survival and pup growth in groups with marked effects on maternal behavior, and reduced weight gain. In vitro findings showed no evidence of mutagenicity (Ames reverse mutation assay & mouse lymphoma cell forward mutation assay), and some evidence of a weak clastogenic response (Chinese Hamster Ovary cells).

5.0 Description of Clinical Data Sources

5.1 Primary Source Data (Development Program)

The primary safety data base is derived from the sponsor's ISS and study reports which describe 2 studies in adults and 3 studies in children. Both studies in adults were bioavailability studies involving single doses. Two of the three pediatric studies were open label multiple dose titration studies, and only one study was a placebo controlled efficacy and safety study. Please see Appendix 1 for a listing of all studies. The sponsor did not provide a final cut-off date in this submission; when asked to provide one, the sponsor stated that all trials were completed at the time of the submission, and that the last patient had completed the final clinical study (Study 04) on 12/15/99 (as per submission of 4/27/00).

5.2 Demographics

The two studies (Studies 01 and 05) performed in healthy adult volunteers included a total of 40 subjects, of which 38 were exposed to the study drug. The majority of subjects were Caucasian males with a median age of 31 years old with the demographic details as follows:

Demographics of Adult Subjects in Studies 01 and 05 (all treated with MPH-MR)

N	40
Median Age; age range	31; 18-50
% male	62.5
% female	37.5
% Caucasian	80
% Black	0.075
% Asian	0.025
% other	0.1

The integrated safety data base for this submission included pediatric patients between the ages of 5 and 14 years old. The sponsor presented data separating the exposure of patients who were treatment naïve and

those with prior exposure to methylphenidate. The following table summarizes numbers of pediatric patients in the submitted database:

	MPH-MR (study drug)	MPH-IR
Treatment Naïve	n=63	n=0
Previous Treatment	n=125	n=25
Total	n=186*	n=25

*n=188 in the sponsor's total ISS count; however, when study report totaled, n=186.

The majority of treatment naïve patients were Caucasian males with a mean age of 8.3 years old, and the majority of patients with prior treatment were Caucasian males with a mean age of 9.6 years old. The table below summarizes the demographics of the pool of all pediatric patients in the integrated safety data base. (Please note that some patients may have been counted multiple times, because of the crossover design of Study 02.)

Demographic Summary of Pediatric Patients (Phase II/III Studies)

Treatment group	MPH-IR	MPH-MR	Placebo
N	25	188	190
Mean Age; age range	9.6; 7-12	9; 6-15	9.3; 5-14
Mean Weight (kg); range	36.9; 26-53	34.4; 18-94	34.3; 19-91
% male	84	82	81.6
% female	16	18	18.4
% Caucasian	88	75	73
% Black	4	12	15
% other	8	13	12

It is noted that males outnumber females in this study population; this is generally tho ught to be reflective of the ADHD population in which, according to the DSM-IV, occurs at a male to female ratio of 4:1 to 9:1. This study sample was predominantly Caucasian.

5.3 Extent of exposure (dose/duration)

In the phase I studies (Study 01 and 05), healthy adult subjects had minimal exposure to the study drug. Study 01 allowed for 3 single exposures of the study drug separated by a week in 18 subjects; a total of 20 subjects were exposed to a single dose. Study 05 exposed 18 subjects to a single dose.

The following is a summary table of dose and duration of exposure in the pediatric population:

Number of Phase 2-3 patients exposed by duration of exposure (either MPH-MR 30:70 or ——

	10-20 mg n=177	25-40 mg n=127	50-60 mg n=45
1-7 days	73	58	28
8-14 days	45	53	16
15-21 days	44	14	1
22-28 days	12	0	0
29-35 days	1	1	0

≥ 36 days	2	0	0
Missing (lost to follow up)	1	0	1

The mean days-exposure (submitted July 7, 2000) from a pooling of all pediatric studies was 20.3 days (s.d.=7.02 days) in 188 patients; thus, exposure for the study drug (including both IR:ER formulations: 30:70 & ——, in pediatric patients is 10.46 patient-years.

The following table summarizes the distribution of age ranges in the NDA safety data base:

Summary of Subjects/Patients by Age Groups for All Studies (01,02,03,04&05)
(adapted from sponsor's submission of 7/7/00)

Age Groups (years old)	# of Ss/Pts
6-9*	234
10-12	113
13-18	10
> 19	39

*One patient who was 5 years old was included in the placebo group.

6.0 Human Pharmacokinetic Considerations

For complete details, please refer to the Clinical Pharmacology and Biopharmaceutics review.

Methylphenidate is known to be easily absorbed, and generally recognized to have a half-life in plasma of 1-3 hours; concentrations in the brain are thought to exceed plasma level. Metabolism for the major metabolite ritalinic acid occurs primarily by the liver.

The sponsor has characterized the following pharmacokinetic properties for Studies 01, 02, and 05 (amended from sponsor's table):

MPH FORM	DOSE/POPULATION	C_{MAX} (NG/ML)	T_{MAX} (HR)	AUC_{INF} (ng.hr/ml)	$T_{½}$ (HR)
MPH-IR	10 mg / adults	4.82	1.9	24.3	2.90
MPH-IR	10 mg bid/adults	6.8	5.2	45.8	2.93
MPH-IR 1st peak 2nd peak	10 mg bid/children	 10.0 11.4	 1.9 7.2	 65.7	
MPH-MR (30:70)	25 mg/adults	3.43 3.40	1.5 8.0	49.9	6.8
MPH-MR (30:70)	20 mg/ children	8.6 9.6	2.2 5.1	63.0	
MPH-MR (30:70)	2 x 20 mg/ children	15.4 17.0	1.8 5.2	119.7	
MPH-MR (30:70)	2 x 20 mg/fed adults	11.723	5.66	116.5	5.00
MPH-MR (30:70)	2 x 20 mg/fasting adults	8.863	4.79	99.72	5.90

It is noted that the sponsor has not characterized the pharmacokinetic properties of the MPH-MR (30:70) formulation at the dosing of 60 mg. However, they were able to provide data for a 60 mg (oral solution), and relative bioavailability of the extended release capsule and the oral solution is almost 100 % in a cross-study comparison at a 40 mg dose.

The sponsor included the following plasma concentration-time curve in the proposed labeling in an attempt

7.0 Review of Efficacy

7.1 Background

For the purposes of this review, there will only be one study reviewed for efficacy, the pivotal study, Study 04. This is the only study that had a comparator control of placebo. The sponsor did administer efficacy assessments in Study 02; however, Period 1 of this study compared placebo and immediate release methylphenidate, and Period 2 was an open label design comparing varying doses and formulations of MPH-MR, the study drug. Therefore, Study 04 is the only study in this NDA data base with an adequate comparator control.

7.2 Review of individual studies

7.2.1 Study MAI 1001-04

Investigators/Location

This multi-site study was conducted in 32 US centers. Please see Appendix 2 for a full listing of the investigators and co-investigators.

Study Plan

Objective(s)/Rationale

The primary objective of the study was to assess the efficacy and safety of this once-a-day dosing formulation of methylphenidate compared to placebo in children diagnosed with attention deficit /hyperactivity disorder (ADHD). A secondary objective was to observe the therapeutic responses to the study drug in the morning and the afternoon.

Population

Patients chosen for this study were physically healthy children aged ≥ 6 years who were diagnosed with ADHD, combined subtype or predominately hyperactive-impulsive subtype according to DSM-IV criteria; children with the primary diagnosis of "ADHD, inattentive type" were not included in this study. Patients were required to demonstrate either an adequate response to standard treatment or a need to be treated with methylphenidate based on the Investigator's assessment; also required was a single teacher able to make morning and afternoon assessments of the child's behavior on days specified in the protocol. Excluded from the study were: 1) females who had reached menarche, 2) patients who had a poor response to methylphenidate or required a third dose in the afternoon or evening, 3) patients with a history of seizure, tic disorder, a family history of Tourette's Disorder, hyperthyroidism, glaucoma, an IQ < 80, or a comorbid psychiatric diagnoses which the investigator felt may interfere with study results (e.g. psychosis, bipolar illness, pervasive developmental disorder, severe obsessive compulsive disorder, severe depressive or anxiety disorder). Prohibited medications during the study were clonidine, anticonvulsants, medications affecting blood pressure or heart rate, medications with CNS effects (e.g. antihistamines, decongestant sympathomimetics), and methylphenidate or pemoline within 30 days prior to the study.

Design

This was a randomized, three week double blind, placebo controlled study with a one week single blind placebo washout. Placebo responders during the wash out period were excluded from the study. Screening included a psychiatric evaluation, history and physical, urinalysis and routine labs. Vital signs were monitored weekly, and physical exam and laboratory tests were repeated at the end of the study.

Assessment instruments during the study include the 10 item Conners' Global Index Scale (see Appendix 3) completed by teachers and parents (referred to as Conners'-Teacher and Conners'-Parent, respectively), the parent version of the NIMH Diagnostic Interview Schedule for Children (used to confirm the ADHD diagnosis), the CGI-I and the Side Effects Rating Form. Efficacy variables utilize the teacher's version of the Conners'-Teachers (filled out three times per week on alternating days in the morning and afternoon) and the parent's version of the Conners'-Parents (completed at morning, afternoon and evening on one day of the weekend during the study). Please see Appendix 4 for the sponsor's schedule of events.

Dosing for patients randomized to the study treatment group started at 20 mg daily during Week 1 and could be titrated up (in increments of 20 mg) to a maximum of 60 mg daily during Week 3 depending on the individual treatment response based on tolerability and optimal efficacy response. Therefore, dosing for the study drug during Week 2 could be either 20 or 40 mg, and, during Week 3, dosing could be 20, 40 or 60 mg of study drug. Dosing was provided three times per day; each dosing consisted of a 20 mg capsule or placebo depending on the total daily dosing. Medications were to be administered before breakfast.

There were two protocol amendments made. The major changes in the first amendment redefined the inclusion criteria to include MPH-naïve patients, provided a severity cut-off for comorbid illnesses of depression and anxiety and eliminated Week 4 of the study. The sponsor also modified the randomization scheme to an "adaptive randomization system" which was later modified in the second amendment back to the original scheme of conventional stratified randomization along. The second amendment also included a clarification of the primary and secondary efficacy variables and analysis plan.

Analysis Plan

The primary efficacy variable was the mean change from baseline of the averaged score from both the morning and afternoon scores of the teacher's version of the Conners' Global Index Scale (see Appendix 3) at Week 3. It should be noted that a higher score on the Conners' Global Index Scale indicates greater pathology, and a higher change from baseline would indicate greater improvement. Secondary efficacy variables included changes from baseline of: 1) the means of the morning and the afternoon score of the teacher's version of the Conners' Global Index Scale, 2) the parent version of the Conners' Global Index Scale (essentially identical to the teacher's version) which was completed on Saturday or Sunday at morning, afternoon and evening, and 3) the CGI-I.

There were no interim analyses performed during this study.

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 507 patients screened, 321 patients were randomized to the double-blind phase of the study; the other patients were disqualified during the single-blind phase of the study. The intent-to-treat population included 314 patients (155 receiving MPH-MR and 159 receiving placebo); reasons for being excluded in the safety population included: lack of dosing or safety data, lack of minimally required efficacy data, and/or lack of adequate dosing. Of the 158 patients randomized to study drug, 141 (89%) completed the study while 83 % of the placebo patients completed the study (135 of 163). Reasons for early withdrawal included: withdrawal of consent (2 of 158 MPH MR patients and 11 of 163 placebo patients) and lack of efficacy (3 of 158 MPH MR patients and 5 of 163 placebo patients). A total of 276 (MPH MR: 141; placebo: 135) patients completed the study.

Demographics /Group Comparability

The majority of patients in this study were Caucasian males. The sponsor separately described patients with no prior drug treatment and patient with a prior drug treatment history as summarized in the following chart (derived from the sponsor's Table 4 of the study report):

Demographics for Study 04

	N	MEAN AGE/RANGE (YEARS)	MEAN WEIGHT/RANGE (KG)
Treatment Naïve Patients			
MPH MR	56	8; 6-13	31; 19-53
Placebo	57	9; 5-12	33; 19-91
Patients with Prior Drug Treatment			
MPH MR	99	9; 6-15	36; 19-94
Placebo	102	10; 6-14	35; 19-91

The mean baseline values for the Connors'-Teacher Scale, Conners'-Parent Scale, and the CGI-I are summarized in the table below. The sponsor provided p-values that did not demonstrate a statistical difference between the baseline values for the study drug and the placebo groups.

Mean Baseline Values of Efficacy Variables

MEAN SCORE	MPH	PLACEBO
Conners'-Teacher*	12.7	11.5
Conners'-Parents	13.6	12.9
CGI-I	4.5	4.4

*Primary efficacy variable

Dosing

Patients were individually titrated to a dose which the principle investigator determined to provide optimal efficacy results and was well-tolerated ranging from 20 to 60 mg day. The following table summarizes the dosing patterns of participants in the study (from Sponsor's Appendix Table 10.1):

Doses Administered for Study 04

WEEK	DOSE MG/DAY	MPH-MR N=155 (%)	PLACEBO N=159
Week 1	20	155 (100)	159 (100)
Week 2	20	58 (37.4)	153 (96.2)
	40	93 (60.0)	
Week 3	20	38 (24.5)	140 (88.1)
	40	59 (38.1)	
	80	43 (27.7)	
Week 4	20		1 (0.6)
	60	1 (0.6)	

Concomitant Medications

At least one concomitant medication was taken by 74 (47.7%) MPH MR patients and 82 (50.9%) in the placebo group. The sponsor listed that the most frequent concomitant medications were acetaminophen for fever or headache, ibuprofen for pain, antihistamines for allergic rhinitis, and anti-asthmatic agents for asthma. One patient was listed as taking clonidine for insomnia (004-017-0003), and another patient (004-004-0001) was listed as taking desyrel for insomnia.

Efficacy Results

For the primary efficacy variable, there was a statistically significant difference (p=<.001) demonstrated when comparing mean change from baseline to Week 3 in the Conners'-Teachers. There did not appear to be any significant difference in the treatment response between previously naïve patients and patients previously treated with methylphenidate.

As a secondary efficacy variable, there was a statistically significant difference seen when comparing placebo and the MPH MR treatment group for the morning and afternoon mean changes of the Conners'-Teachers. The sponsor presented the following summary table (from sponsor's Table 7 in the study report):

Mean change from baseline of Conners'-Teacher, morning/afternoon groups, by week

Week	Time	MPH MR	PLACEBO	P VALUE
1	AM	5.7	0.8	<0.001
	PM	5.1	0.2	<0.001
2	AM	7.3	1.0	<0.001
	PM	7.0	0.4	<0.001
3	AM	8.3	1.6	<0.001
	PM	7.7	1.1	<0.001

For other secondary efficacy variables, the sponsor also reported a statistically significant finding ($p < 0.001$) for both the change from baseline to the end of Week 3 for the Conners'-Parents and the CGI-I.

Dr. Kallappa M. Koti, FDA statistical reviewer (preliminary review: 4/4/00) further analyzed the sponsor's data and made the following conclusions:

1. The baseline values for the primary efficacy variable for the two treatment groups were comparable.

2. There was no statistical significance found for differences in the primary endpoint for the variables of site, gender, race, or previous treatment. One interesting note is that a statistically significant difference was observed when comparing the treatment naïve and previous treatment groups with methylphenidate at the end of Week 1, i.e. the group of treatment naïve patients had a higher change from baseline at week 1 than the previously treated group. However, no differences in response were observed between these two groups after Week 1.

3. There is a marginally significant difference (p-value = 0.0543) when examining the variable of weight for the change from baseline of the primary efficacy variable. Dr. Koti was able to demonstrate that patients with a higher body weight tended to have a lower change from baseline. Dr. Koti generated the following table (using a cut off at 31.4 kg) which shows the mean change from baseline for these two groups separated by dosing:

Change from baseline in Week 3 for Conners'-Teacher (from Dr. Koti's review)

	WEIGHT	
	< 31.4 kg	≥ 31.4 kg
Placebo	1.32	1.11
MPH 20 mg	7.51	5.96
MPH 40 mg	9.56	6.2
MPH 60 mg	9.72	8.6

As can be seen from Dr. Koti's table above, a greater improvement was observed in the Conners'-Teacher scale for the lighter weight children. Dr. Koti also notes in his review that although there is a statistically significant difference between these two groups (i.e. < 31.4 kg and ≥ 31.4 kg), both groups independently demonstrated superior results when compared to placebo. One possible explanation for these findings is that the larger weighted children could have benefited from a higher dosing regimen. However, Dr. Koti did not find any relationship between dose and weight ($p=0.56$).

4. Findings from the secondary efficacy variable of the mean changes from baseline of the morning and afternoon scores from the Conners'-Teacher demonstrated that there appeared to be less improvement in the afternoon scores when compared with the morning scores. However, as noted above, statistical significance is demonstrated when comparing the morning or afternoon scores to placebo.

7.3 Miscellaneous Issues

During the site audit for Study 04, it was noted by the inspector that no supporting documents were seen for three patients (Subjects # 15, 18, 19). It was recommended by the reviewer in DSI that these subjects not be used in support of this NDA. This was discussed with the FDA statistical reviewer Dr. Koti and Dr. Tom Laughren, psychiatry team leader, who agreed that a reanalysis excluding these subjects was probably unnecessary at this time in light of the large degree of statistical significance demonstrated in this trial and the high power of the study.

7.4 Conclusions

The results of Study 04, the pivotal study, provide evidence that Metadate MR is effective in the treatment of children diagnosed with ADHD.

8.0 Integrated Review of Safety

8.1 Background and Methodology for Safety Review

The sponsor submitted the integrated safety database of all five studies conducted with the study drug, methylphenidate hydrochloride Modified-Release capsules (MPH-MR). In Study 01 (adults), there were three formulations studied in adults with the following differing ratios of immediate release:modified release (IR:MR): [redacted] 30:70 and [redacted] Study 02 (children) utilized the IR:MR formulations of 30:70 and [redacted] while Studies 04 (children) and 05 (adults) utilized the IR:MR formulation of 30:70. Study 04 was the only study design with a placebo control parallel to the study drug; there were no trials conducted with a design in which a comparator control of MPH-IR was administered in parallel to the study drug.

It is noted that the sponsor's only bioavailability study (Study 04) conducted in the target population of children for MPH-MR (IE:MR = 30:70) was at doses of 20 and 40 mg; the 60 mg dose (the maximum dose in proposed labeling) was not studied and the pharmacokinetic properties were not explored in this NDA submission.

There were a total of 396 individuals included in the entire integrated safety database; this includes 40 healthy adult subjects in bioavailability studies (01 & 05). The Phase II/III studies included 356 pediatric patients of which 186 were exposed to study drug. The only parallel placebo controlled safety and efficacy study was three weeks in duration (Study 04) and included 158 patients on study drug and 163 patients on placebo in the following age break down:

Summary by age group of Study 04 (submitted 6/9/00)

AGES (YRS)	MPH		PLACEBO	
	N	(%)	N	(%)
6-9*	110	(69.6)	106	(65)
10-12	43	(27.2)	53	(32.5)
13-18	5	(3.2)	4	(2.5)

*Includes one 5 y.o. patient (unclear which group)

# of days exposed to MPH-MR by dose level for Study 04 (submitted 6/9/00)

Dose	Mean Days
MPH 20 mg	11.57
MPH 40 mg	9.58
MPH 60 mg	7.56
Total	20.47

Please refer to Section 5.3 for summaries of drug exposures for the entire NDA data base.

8.2 Deaths/Other serious adverse events

There were no deaths or other serious adverse events reported in this NDA data base.

8.3 Assessment of Dropouts

8.3.1 Overall pattern of dropouts

The following table (adapted from sponsor's submission) summarizes the overall drop out pattern for pediatric patients (studies 02, 03, and 04):

Summary of Dropouts

Treatment Group:	Placebo N=190	MPH-IR N=25	MPH-MR 188	Total MPH (IR MR) 189
# Completed (%)	158 (83)	23 (92)	169 (90)	169 (89)
# Withdrawal (%)	32 (16.8)	2 (8)	19 (10)	20 (11)
# Dropout by Termination reason				
Lost to f/u	2 (1.0)	0	1 (0.5)	1 (0.5)
Personal Reason	12 (6.3)	1 (4.0)	3 (1.6)	3 (1.5)
Noncompliance	5 (2.6)	0	3 (1.6)	3 (1.6)
Adverse Event	0	0	2 (1.1)	2 (1.0)
Other	6 (3.2)	0	7 (3.7)	7 (3.7)
Lack of Efficacy	5 (2.6)	0	3 (1.6)	3 (1.6)
Unable to tolerate placebo	2 (1.0)	1 (4.0)	0	1 (0.5)

As can be seen from the table above, and as might be expected, the completion rate was higher for both methylphenidate formulations than for placebo. Both the immediate release and the modified release formulation of methylphenidate had comparable dropout rates. The most frequent reason for dropouts according to the table above was for "other" and "personal reason"; the sponsor did not elaborate on the details of these categories.

8.3.2 Adverse Events Associated with Dropout

There were two subjects who withdrew due to an adverse event; both were in Study 04 and were receiving the study drug. Two other patients withdrew prior to receiving the study drug. The table below summarizes all patients who withdrew due to an adverse event.

Patients who dropped out due to adverse event

PATIENT #	AGE (YRS)	GENDER	DAYS ON STUDY DRUG	EVENT
Study 04: Center 05 Subject 0003	10	Male	6	**Rash**: pruritic, nonerythematous periumbilical. Recovery after discontinuation. Concomitant medication included Flovent MDI for asthma.
Study 04: Center 35 Subject 0015	9	Female	5	Day 4: **headache**; Day 5: **stomachache** and **dizziness**. Concomitant medications: budesonide and cetirizine for allergic upper airway disease.
Study 04: Center 25				Withdrawn prior to randomization due to elevated ALT level during placebo run-in.
Study 004 Center 25 Subject 0006				Low eosinophil count prior to receiving randomized medication.

8.4 Other Safety Findings

8.4.1 Adverse Event Incidence

When the sponsor pooled all studies together, it was found that of the 229 subjects and patients exposed to the study drug, 126 (55%) reported at least one adverse event, and, while taking placebo, 38.4% (73 of 190) individuals reported at least one adverse event. The most common adverse events reported in ≥ 5 % of patients in the pediatric studies (Studies 02, 03, 04) are summarized in the following table from the sponsor's ISS:

Adverse events noted in ≥5% of patients with ADHD receiving placebo or MPH-MR (30:70 &—— (Pooling of all pediatric studies: 02, 03, 04)

	Placebo	MPH MR Maximum Daily dose			
	(N=166)	10-20 mg N=61 (%)	25-40 mg N=82 (%)	50-60 mg N=45 (%)	Total N=188 (%)
Overall Events					
Subjects with at least one AE	61 (36.7)	35 (57.4)	51 (62.2)	18 (40.0)	104 (55.3)
Total number of AEs	105	66	100	36	202
Specific Events					
Body As a Whole	47 (28.3)	22 (36.1)	38 (46.3)	17 (37.8)	77 (41.0)
Abdominal pain	8 (4.8)	3 (4.9)	11 (13.4)	3 (6.7)	17 (9.0)
Headache	16 (9.6)	10 (16.4)	10 (12.2)	5 (11.1)	25 (13.3)
Digestive system	19 (11.4)	14 (23.0)	21 (25.6)	6 (13.3)	41 (21.8)
Anorexia	4 (2.4)	7 (11.5)	11 (13.4)	3 (6.7)	21 (11.2)
Nervous System	12 (7.2)	15 (24.6)	20 (24.4)	5 (11.1)	40 (21.3)
Dizziness	0	3 (4.9)	2 (2.4)	1 (2.2)	6 (3.2)
Insomnia	4 (2.4)	4 (6.6)	6 (7.3)	3 (6.7)	13 (6.9)

Note: This is Table 14 in sponsor's ISS and has been reviewed for accuracy.

In order to better characterize the safety of this study drug, it would be most helpful to examine the adverse events profile generated in Study 04 which is the only controlled study assessing placebo and the study drug. The following table summarizes adverse events occurring in ≥ 1% of patients in Study 04:

Adverse Events reported by ≥ 1% of MPH-MR patients in Study 04 (placebo controlled study)

COSTART Body System	COSTART Preferred Term	MPH MR N = 155 (100%)	Placebo Subjects N = 161 (100%)	χ^2 P-value
Body as a whole	Abdominal pain	15 (9.7)	8 (5.0)	0.107
	Head-ache	23 (14.8)	17 (10.6)	0.253
	Accidental injury	2 (1.3)	3 (1.9)	0.683
	Fever	2 (1.3)	3 (1.9)	0.683

	Flu syndrome	4 (2.6)	3 (1.9)	0.665
	Infection	5 (3.2)	7 (4.3)	0.602
Digestive	Anorexia	15 (9.7)	4 (2.5)	0.007
	Diarrhea	2 (1.3)	2 (1.2)	0.970
	Gastroenteritis	3 (1.9)	0 (0.0)	0.076
	Nausea	3 (1.9)	3 (1.9)	0.963
	Vomiting	2 (1.3)	8 (5.0)	0.062
Metab./ Nutrition	Weight loss	3 (1.9)	0 (0.0)	0.076
Nervous	Insomnia	11 (7.1)	4 (2.5)	0.054
	Depression	2 (1.3)	0 (0.0)	0.148
	Somnolence	2 (1.3)	2 (1.2)	0.970
Special senses	Conjunctivitis	2 (1.3)	2 (1.2)	0.970

The most significant differences between placebo and study drug for the events of anorexia (p=0.007), insomnia (p=0.054), vomiting (p=0.062), gastroenteritis (p=0.076), and weight loss (p=0.076). The sponsor lists headache, abdominal pain, anorexia, and insomnia as the most common adverse events observed in Study 04 occurring in over 5% of the MPH-MR patients.

Anorexia occurred almost four times as frequently in the MPH-MR group compared to placebo in Study 04, demonstrating a statistically significant difference (p=0.007). It is also noted that in Study 02, when doses were given after food intake, appetite loss was observed in the following proportions: placebo group: 29%; MPH-IR group: 48%, MPH-MR group: 50-73 %. Concerns regarding anorexia become especially relevant, because the labeled instructions recommend dose administration prior to breakfast, which may increase the effect of appetite suppression.

8.4.2 Laboratory Findings

Post baseline laboratory values were not collected in adult studies (Studies 01 and 05).

For the other studies (02, 03, 04), the protocols in this submission described post baseline data for the following laboratory values: **Biochemistry:** SGOT, SGPT, Alkaline Phosphate, Bilirubin, Creatinine, blood urea nitrogen (BUN); **Hematology:** Hemoglobin, Hematocrit, WBC, Eosinophils, Platelet Count; **Urinalysis:** Glucose, Protein.

This submission did not provide values of central tendency of laboratory values in either the ISS nor the individual study reports. In the ISS, the sponsor summarized the number of patients whose post baseline labs values increased, decreased, or remained unchanged, and also provided laboratory values that were out of the range of normal; baseline values were not listed unless they were out of normal range.

A visual scanning of the ISS laboratory data (ISS: Vol. 44: Table 5.3)did not reveal any obvious differences between the MPH-IR, MPH-MR (the study drug) and placebo groups. However, of note was the change in neutrophil count of one patient (Subject # 004-023-0012: age and gender not located in this submission) whose total white blood count was unremarkable:

	Screening	Final	NL Range
WBC (x 10^6/L)	5900	6200	4100-1230
Neutrophils			
(%)	35.5%	16.0%	40.9-60.0
(x 10^6/L)	2094	992	

It can be seen that this patient was already in an low abnormal range at base line; however, the "final" neutrophil count could be characterized as moderate neutropenia. It would be helpful to obtain follow up data for Subject #004-023-0012 in an attempt to assess if this was a drug related effect. In the ISS Summary Table 16 (pooling of studies 02, 03 and 04) neutrophil counts changed from "normal to low" in 16 (of 190) placebo patients, and 11 (of 188) patients in the MPH-MR groups, while 0 (of 25) patients in the MPH-IR group demonstrated a normal to low change from baseline of neutrophil count. There were also no significant patterns observed in the neutrophil and WBC labs when comparing study drug and placebo in the placebo controlled Study 04 (see table below).

The following sponsor table summarizes the number of patients from Study 04, the pivotal placebo controlled study, who had within-range baseline value and an out of range post-treatment value:

Summary of out-of-reference range post-treatment laboratory test results (copied from Sponsor's Table 16 from Study Report for Study 04)

Lab	Number (%) of Subjects With Within-Range Baseline Values & Out-of-Range Post-Treatment Values	
	MPH MR (N=155)	Placebo (N=161)
Hematology		
Hemoglobin	1 (0.6)	1 (0.6)
RBC	0 (0.0)	1 (0.6)
WBC	3 (1.9)	3 (0.02)
Platelet Count	1 (0.6)	0 (0.0)
Lymphocytes	1 (0.6)	0 (0.0)
Eosinophils	10 (6.5)	17 (10.6)
Neutrophils	9 (5.8)	12 (7.5)
Monocytes	2 (1.3)	3 (1.9)
Basophils	1 (0.6)	1 (0.6)
Atypical Lymphocytes	0 (0.0)	1 (0.6)
Biochemistry		
AST	2 (1.3)	2 (1.2)
Total Bilirubin	3 (1.9)	1 (0.6)
Alkaline Phosphatase	2 (1.3)	1 (0.6)
Glucose	0 (0.0)	1 (0.6)
Potassium	0 (0.0)	1 (0.6)
PA Osmolarity	0 (0.0)	1 (0.6)
Urinalysis		
Specific Gravity	5 (3.2)	13 (8.1)
Protein in urine	8 (5.2)	4 (2.5)

The sponsor identified seven of the above patients who demonstrated a change from baseline determined to have possible clinical significance based entirely on the discretion of individual investigators. One of these cases (Subject No. 0019) was listed as an adverse event, as a urine protein at baseline was found to have increased to 30 mg/dl post-treatment. The only other significant change was an elevation in eosinophil counts observed in five patients in Study 04 of which three were in the MPH group and two were in the placebo group; no clinical signs or symptoms were reported for these patients.

The sponsor reported that there was no evidence of a dose-related effect for laboratory test, and that lab changes with methylphenidate at all doses were comparable to placebo. It is noted that there were no dropouts due to laboratory results after randomization to a study group (See Section 8.3.2 above).

8.4.3 Vital Signs

Vital signs including sitting systolic and diastolic blood pressure, pulse and temperature were collected in all studies. In the ISS, the sponsor demonstrated that the mean changes of systolic and diastolic blood pressure, pulse and temperature were comparable for all study groups within each study.

In order to establish a comparator control, it is helpful to examine Study 04, the placebo controlled pivotal study, in more depth. The following is a table summarizing the collection of blood pressure and pulse in Study 04:

	Sys. BP mean (range)	Dias. BP mean (range)	Pulse mean (range)
Placebo (n=161)			
Baseline	101.2 (80, 128)	62.6 (43, 80)	81.7 (52, 110.0)
Wk 1	102.0 (78,130)	64.0 (42,90)	82.9 (60, 108)
Wk 2	102.0 (78, 124)	62.9 (45, 80)	81.8 (60, 116)
Wk 3	102.0 (82, 180)	62.6 (40, 82)	82.6 (60, 112)
MPH-MR (n=155)			
Baseline	102.2 (76, 128)	63.5 (40, 90)	82.3 (60, 115)
Wk 1	101.4 (80, 124)	64.2 (45, 90)	82.8 (60-111)
Wk 2	102.1 (78, 128)	63.6 (40, 100)	82.4 (56, 110)
Wk 3	103.2 (86.0, 133)	64.3 (44, 98)	84.1 (56, 120)

As can be seen above, the mean systolic blood pressure did not differ appreciably between the placebo and the treatment group. Although the maximum baseline diastolic bl ood pressure is 10 mm Hg higher in the study drug group compared to the placebo group, the maximum values for the treatment group surpass the placebo group by 16 and 20 mm Hg during Week 2 and Week 3, respectively. This may indicate that the study drug, MPH-MR, has the potential to increase the diastolic blood pressure. With the except of Week 2, the mean pulse rate was shown to be slightly higher in the treatment group compared to the placebo group.

As a method of assessing outliers, the sponsor determined the following percentages of patients who had post-treatment values above the 95 th percentile using the age appropriate criteria established for this pediatric population in Study 04:

	MPH-MR (N=155)	Placebo (N=161)
Sys. BP > 95 percentile	8 (5.2%)	7 (4.3%)
Dias. BP > 95 percentile	4 (2.6%)	3 (1.9%)

Temperatures measured in Study 04 did not differ appreciably between treatment groups.

The sponsor did not report weights in this submission.

8.4.4 Electrocardiograms

No electrocardiograms were obtained during the development of this drug.

8.4.5 Withdrawal reactions and abuse potential

The sponsor did not request a change in scheduling. Therefore, this methylphenidate formulation would be a Schedule II classification as other methylphenidate drug products.

8.4.6 Human Reproduction Data

No data was submitted addressing the effects of methylphenidate on human reproduction.

8.4.7 Overdose experience

The sponsor did not report any incidents of overdose. The proposed labeling contains the standard language as is currently written in the Ritalin (methylphenidate) labeling.

8.4.8 Literature

A review of the literature was not required in this submission, as this application was filed under section 505(b) 2, and methylphenidate has a long marketed history. The sponsor did not submit a literature review.

8.5 Adequacy of patient exposure and assessments

Based on the fact that methylphenidate has a long history of being marketed, the exposure for this specific formulation could be considered adequate. Of some concern is that the sponsor has not characterized the pharmacokinetics of the ———————— . as this is a new combination and formulation of a mixture of the immediate and extended release forms. However, the sponsor may have submitted enough data to compensate for this omission in their data base (please refer to the Clinical Pharmacology and Biopharmaceutics review).

Because there was no central tendencies presented for the laboratory values, it was difficult to determine trends and outliers. It would be helpful to have follow up information on the one patient (Subject #004-023-0012) who demonstrated a moderate neutropenia.

9.0 Financial Disclosure

The sponsor submitted a certification of Financial Interests and Arrangements of Clinical Investigators. The Chief Operating Officer signed the Form 3454 testifying that, to his knowledge, there was no financial arrangement made with investigators that could affect the outcome of the study as defined in 21 CFR 54.2 (a), and that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). No disclosures could be collected from five individual investigators/subinvestigators who were no longer working at the study site.

10. Conclusions

Efficacy

This formulation of methylphenidate-modified release has been shown to be effective in the treatment of ADHD in the pediatric population when administered in the morning before breakfast. Effectiveness has been demonstrated in the morning and in the afternoon when both time periods were compared to placebo. A review of the data demonstrates that there is a greater treatment effect in the morning than the afternoon; however, this difference was not shown to be statistically significant.

Safety

The safety findings in this review were consistent with findings previously reported in the literature and labeling of currently marketed methylphenidate formulations. There were no safety findings that would impede the marketing of this formulation of methylphenidate.

Of some consideration, though, is the finding that anorexia occurred more frequently in a group receiving the study drug when compared to placebo in the placebo controlled Study 04 (see Section 8.4.1 above). Concerns regarding anorexia become especially relevant, because the proposed labeling recommends dose administration prior to breakfast. Even though it is recognized that f ood has been demonstrated to affect the bioavailability and absorption of this formulation of methylphenidate, clinically, dosing prior to breakfast may increase the effect of appetite suppression.

Also of safety consideration is that the sponsor did not assess weight changes in this database. It would be most helpful to assess weight changes over a longer duration of time; especially in light of the fact that ADHD can present as a chronic illness, and medication treatment for some may be extended far beyond one year.

Labeling

It appears that the sponsor has used the labeling for Ritalin (methylphenidate) as the model for their proposed labeling. A more recent update of the methylphenidate labeling was written for the marketing of Concerta ™ (methylphenidate HCl); it is recommended that many of the stylistic changes made (i.e. clear headings, etc.) also be adopted for the labeling of this formulation of Metadate.

Other suggestions are as follows:

1. In the **CLINICAL PHARMACOLOGY** Section:

- [ ]
- [ ]

2. In the **CLINICAL STUDIES** Section:

This section is written in very vague terms, and it is recommended that the following clarifications be incorporated into the labeling:

- [redacted] It would also be more informative for the sponsor to include the name of the primary efficacy variable (i.e. the Conners' Global Index Scale) which is widely recognized as an instrument to assess ADHD symptomatology.

- Although efficacy was shown for the morning and afternoon for the study drug compared to placebo, the statement "[redacted]." is not an accurate statement. As stated in the FDA statistical review by Dr. Koti, the mean changes from baseline of the morning and afternoon scores from the Conners' Global Index Scale-Teacher (a secondary efficacy variable) demonstrated less improvement in the afternoon scores when compared with the morning scores. However, statistical significance was demonstrated when comparing the morning or afternoon scores to placebo.

- Also, the language in the labeling should specifically state what parameter "showed a statistically significant improvement in symptom" (i.e. mean change from baseline of the averaged score from both the morning and afternoon scores of the teacher's version of the Conners' at the end of Week 3).

3. In the **INDICATIONS AND USAGE** Section:

- The sponsor has not provided any efficacy data for the indication for [redacted], and it is recommended that this be removed from the labeling.

4. In the **CONTRAINDICATIONS** Section:

- Concomitant use of Monoamine Oxidase Inhibitors should be added.

5. In the **PRECAUTIONS** Section:

- Under **Pregnancy Category**: Given new pre-clinical findings, methylphenidate has been recategorized as Pregnancy Category C, and it is recommended that this labeling reflect that change.

- Under **Pediatric Use**: It is recommended that the statement "long term effects of methylphenidate in children have not been well established" be added.

11. Recommendations

It is recommended that this NDA receive an "approvable" action. Because this formulation of methylphenidate is recommended to be administered prior to meal time, it would be important for the sponsor to monitor the adverse event of anorexia or loss of appetite in a Phase IV study, or alternatively assess if this formulation is also effective if administered with food.

Roberta L. Glass, M.D.
Medical Officer, Division of Neuropharmacological Drug Products

NDA 20-825
Div File
HFD-120: Katz/Laughren/Homonnay/Glass

Appendix 1

Summary of extent of exposure to study drug (Amended from Sponsor's Table 5 from ISS)

	Description	Drug(s) Tested/Regimen	Number of Subjects	Treatment Duration
Study 01	Bioavailability study; 6 treatment crossover in healthy **adult** volunteers	Ritalin® 10 mg (1dose); Ritalin® 10 mg (2 doses in one day); Ritalin® SR 20 mg (1 dose); MPH MR [redacted] 1 dose) 25 mg dose; MPH MR 30:70 (1 dose); MPH MR [redacted] dose).	Total: n= 22 **Study drug: n=20**	Single dose or 2 dose session spaced 1-2 weeks apart.
Study 02	Double-blind, placebo-controlled (to MPH-IR only) 4 treatment crossover study in **children** with ADHD	All patients received treatments a and b for one week and then either c and d or e and f.: a. MPH IR 10 mg *bid*; b. Placebo, *bid*; c. MPH MR 30:70, 20 mg/day; d. MPH MR [redacted] 20 mg/day; e. MPH MR 30:70, 40 mg/day; f. MPH MR [redacted] 40 mg/day.	Study drug: n=25 a. 25 b. 27 c. 13 d. 13 e. 12 f. 11	4 treatments, 1 week each.
Study 03	Open label dose titration study in **children** with ADHD.	MPH MR 30:70. Starting daily-dose, 10 mg/day; escalation in 10 mg/day increments to a maximum of 60 mg/day.	Total n=8 **Study drug: n=6**	6 weeks
Study 04	Double-blind, placebo-controlled parallel group study in **children** with ADHD.	a. MPH MR 30:70, 20, 40, 60 mg/day; b. Placebo	a. 158 b. 163 **Study drug: n=155**	3 weeks
Study 05	Bioavailability crossover study of fasting dose and dose after high fat meal in healthy **adult** volunteers.	MPH MR 30:70, single 40 mg dose (2 x 20 mg capsules).	18	2 single doses spaced at least 1 week apart.
Totals: Studies -01 and -05 (bioavailability studies in adult healthy volunteers): Total: n=40; Study Drug: n=38 Studies -02, -03, -04 (Phase II and III studies in ADHD pediatric patients): Total: n=356; Study Drug: n=186 **Total (all studies)** n=396 subjects of which **186 where exposed to the study drug.**				

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APPENDIX 3

10 item Conners' Global Index Scale-Teacher's version
(from sponsor's submission)

Student's Name_____ Gender: M F
(circle one)

Birthdate: ___/___/___ (Month Day Year) Age:_____ School Grade:_____

Teacher's Name:_____ Today's Date: ___/___/___ (Month Day Year)

Instructions: Below are a number of common problems that children have. Please rate each item according to how much of a problem it has been in the last month [or other applicable time unit]. For each item, ask yourself, "How much of a problem has this been in the last month [or other applicable time unit]?" and circle the best answer for each one. If none, not at all, seldom, or very infrequently, you would circle 0. If very much true, or it occurs very often or frequently, you would circle 3. You would circle 1 or 2 for ratings in between. Please respond to all items.

		NOT TRUE AT ALL (Never, Seldom)	JUST A LITTLE BIT TRUE (Occasionally)	PRETTY MUCH TRUE (Often, Quite a Bit)	VERY MUCH TRUE (Very Often, Very Frequent)
1.	Temper outbursts; explosive, unpredictable behavior...	0	1	2	3
2.	Excitable, impulsive.....	0	1	2	3
3	Restless or overactive.....	0	1	2	3
4.	Cries often and easily.....	0	1	2	3
5	Inattentive, easily distracted.....	0	1	2	3
6	Fidgeting.....	0	1	2	3
7.	Disturbs other children.....	0	1	2	3
8.	Demands must be met immediately—easily frustrated.	0	1	2	3
9.	Fails to finish things he/she starts.....	0	1	2	3
10.	Mood changes quickly and drastically.....	0	1	2	3

APPENDIX 4
Sponsor's Schedule of Events for Study 04

SCHEDULE OF EVALUATIONS BY VISIT

	SCREENING[a]	ORIENTATION	BASELINE	DOUBLE-BLIND TREATMENT		
PRECEDING WEEK NUMBER:	[-"a" to -1]	[-1]	0	1	2	3
VISIT:	V_S	V_O	V_B	V_{E1}	V_{E2}	V_{E3}
STUDY ACTIVITY:						
CONSENT/ASSENT FORM	X					
MEDICAL HISTORY	X					
PHYSICAL EXAM	X	X[e]				X
VITAL SIGNS[b]	X	X[e]	X	X	X	X
LABORATORY TESTS	X					X
PSYCHIATRIC EVALUATION	X					
DISC INTERVIEW			X			
REVIEW EXCLUSION CRITERIA[c]	X	X	X			
DISPENSE SINGLE-BLIND PLACEBO		X				
DISPENSE DOUBLE-BLIND MEDICATION			X	X	X	
ASSESS ADVERSE EVENTS			X	X	X	X
REVIEW MEDICATION LOG & RETURNED MEDICATIONS			X	X	X	X
CLINICAL GLOBAL IMPRESSION		X	X	X	X	X
10-ITEM CONNERS' GLOBAL INDEX[d]		X	X	X	X	X
SIDE EFFECTS RATING SCALE		X	X	X	X	X
ADVERSE EVENT(S)			X	X	X	X

a - Procedures scheduled for the Screening Visit may be performed on more than one day *before or the day of the Orientation Visit*.
b - Sitting blood pressure, pulse, temperature, and weight will be collected at each visit. Height will only be measured at the Screening Visit.
c - Patients who are determined to be placebo responders are not eligible.
d - 10-item Conners' Global Index refers to both the parent version and the teacher version (see protocol Section 5.3.1)
e - The vital sign and physical exams must be repeated only if the Screening Visit occurs prior to rather than on the same day as the Orientation Visit.

/s/

Roberta Glass
12/7/00 03:55:13 PM
MEDICAL OFFICER

Thomas Laughren
12/23/00 10:44:45 AM
MEDICAL OFFICER
I agree that we can proceed with an approvable action. See memo to fi
le for more detailed comments.--TPL