CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-121

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

APPLICATION INFORMATION
NDA: 20-121
Sponsor: Alza Corporation
Date submitted: July 15, 1999
Date received: July 19, 1999
User fee due date: May 19, 2000
DRUG NAME
Drug: OROS methylphenidate HCl tablets(18 and 36 mg)
Proposed Trade Name: Concerta
DRUG CATEGORIZATION
Pharmacological Class: Psychostimulant
Proposed Indication: Attention Deficit Disorder
Dosage Forms: 18 and 36 mg extended release tablets
Route: Oral
REVIEWER INFORMATION
Medical officer: Andrew Mosholder, M.D.
Completion Date: March 23, 2000

Contents

1.0 Material Used in Review

Original NDA submission 1/15/99
NDA 4 month safety update
NDA 7 month safety update
Case report forms 39011, 159028
Consultation from Dr. Michael Klein of HFD-170 regarding abuse potential
Consultation from OPDRA regarding proposed proprietary name
Consultation from Dr. Raymond Joseph of HFD-180 regarding adverse gastrointestinal reactions

2.0 Background

2.1 Indication

The following drug products are indicated for the treatment of attention deficit disorders, referred to as Attention Deficit/Hyperactivity Disorder (ADHD) in the DSM-IV.

Dexedrine (d-amphetamine sulfate) and Dexedrine Spansule sustained release capsules
Adderall (amphetamine and d-amphetamine, various salts)
Ritalin (methylphenidate HCl) and Ritalin SR sustained release tablets
Cylert (magnesium pemoline)
Desoxyn (methamphetamine HCl)

All of the above are considered psychostimulants, and are controlled substances with category II designations (except for Cylert, which is category IV). It will be seen from the above that there are sustained release formulations approved for d-amphetamine and methylphenidate; a previously marketed sustained release formulation of methamphetamine has been discontinued recently. Only one of these drugs, pemoline (Cylert), was approved after the amendments to the Food Drug and Cosmetic Act requiring efficacy studies; the other drugs were granted this indication under the DESI process.

With respect to sustained release Ritalin, this was approved without efficacy trials, and some have suggested that its efficacy is not as robust as immediate release Ritalin, possibly due to insufficient Cmax values, or to tachyphylaxis of the stimulant effect (see Swanson et al. Clin Pharmacol Ther 1999;66:295-305).

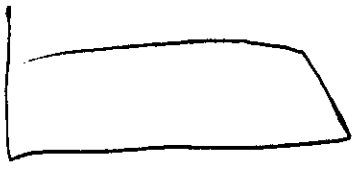
The rationale for this drug product is to provide a once-a-day dosage formulation for methylphenidate (MPH) that sustains the attention-improving effects through the course of the day. This would avoid a second dose at noon, which is traditionally how immediate release MPH is administered. The requirement for a second dose during school hours is regarded as a major limitation for immediate release MPH.

2.2 Related INDs and NDAs

The IND [redacted] Some related INDs and NDAs for methylphenidate are listed below (this may not be a complete listing).

Ritalin (NDA 10-187 Novartis)

Ritalin SR (NDA 18-029 Novartis)



2.3 Administrative History

The original IND submission for this drug product was submitted 11/14/97, and the IND was allowed to proceed.

An End of Phase II meeting between Division of Neuropharmacologic Drug Products staff and Alza representatives was held 8/20/98. Please refer to the minutes of that meeting for details. On 1/8/99 Alza wrote to the Division with questions about how to obtain a comparative efficacy claim for OROS MPH with respect to Ritalin. The Division answered in a letter dated 2/24/99, stating that a therapeutic equivalency claim was unlikely to result from the development program in progress. Please refer to this letter for details.

2.4 Proposed directions for use

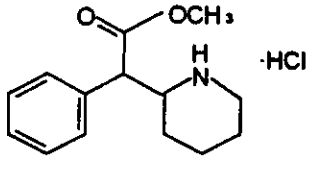
The indication in the sponsor's draft labeling is for ADD, as part of a comprehensive treatment plan; this is taken from the approved Ritalin labeling. The OROS MPH is to be taken once daily in the morning, with or without food, and should not be chewed or crushed. For methylphenidate naïve patients the starting dose is 18 mg. For patients already taking methylphenidate the conversion to OROS daily dosage is listed in the labeling as follows:

MPH 5 mg BID-TID	or Ritalin SR 20 mg	=	18 mg
MPH 10 mg BID-TID	or Ritalin SR 40 mg	=	36 mg
MPH 15 mg BID-TIID	or Ritalin SR 60 mg	=	54 mg

The proposed trade name is Concerta. This name is acceptable to OPDRA (please refer to the consultation from OPDRA dated 9/13/99).

3.0 Chemistry

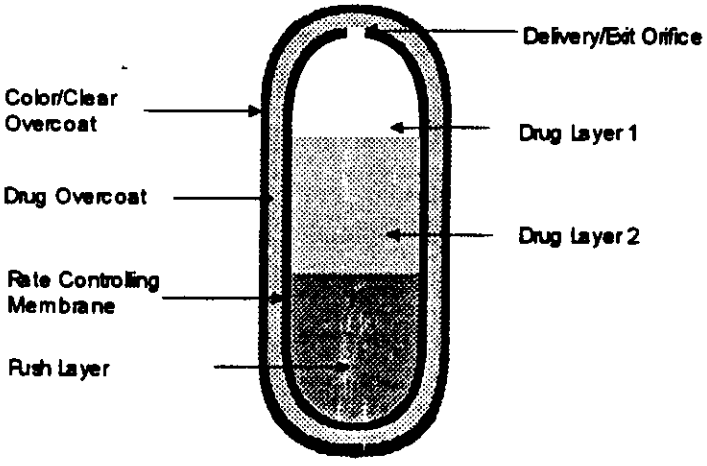
The structural formula for methylphenidate is shown below. The chemical name is *threo*-(±)-methyl-α-(2-piperidyl) acetate.



From the above, it will be seen that there are two asymmetric carbons in the structure of methylphenidate. The marketed compound is a racemic mixture of + and – threo enantiomers.

This drug product has an outer coat containing methylphenidate that is released immediately, and an inner core also containing methylphenidate for extended release. As the inner "push layer" of polymer excipients absorbs water and expands, the drug-containing material is pushed out of the minute orifice at the end of the capsule. The intended result is that some of the drug substance is released immediately from the outer coat, and the remainder is released through osmotic action over a longer period of time. There are two drug layers within the tablet, containing different amounts of drug substance (more in the second layer), and thus the amount of methylphenidate released increases as the first layer is depleted and the next layer begins to be expelled. In this way the release rate of methylphenidate is controlled as the tablet progresses through the GI tract.

Below is a diagram of the OROS product, reproduced from the NDA submission. Alza has formulated two tablet strengths for marketing: The 18 mg tablet contains 4 mg methylphenidate in the outer coat and 14 mg in the core, and the 36 mg contains 8 mg methylphenidate in the outer coat and 28 mg in the core.



4.0 Preclinical data

New preclinical data on methylphenidate cited in this submission include the following. A reproductive toxicity study in mice showed no impaired fertility; in addition, a reproductive toxicity study in rats showed no impairment of fertility or evidence of teratogenicity. Also, a gastrointestinal irritation study in which beagles received the OROS methylphenidate product showed no evidence of lesions in the GI tract.

5.0 Clinical Data Sources

According to the sponsor's ISS, the primary safety database for this application comprises 8 studies in pediatric patients with ADHD and 9 studies in normal adult volunteers. The information presented here is based on the original NDA submission and the 4 month and 7 month safety update submissions. For the 7 month (i.e., the latest) safety update, the cutoff date for submission of safety data was 10/31/99. For ease of review, the 7 month safety update data was presented in a cumulative fashion, incorporating all the previous safety data.

The demographic information for the healthy volunteers is summarized below. Subjects in the Phase I type studies were predominantly caucasian males with a median age of close to 30 years.

Treatment group	OROS	Ritalin immediate release	Ritalin SR
N	286	113	59
% male	66.4	81.4	64.4
% female	33.6	18.6	35.6
Median age	27	29	27
% Caucasian	79.0	91.2	83.1
% Hispanic	9.1	7.1	13.6
% Black	7.7	0.9	1.7
% Asian	2.8	0.9	1.7
% Other	1.4	0	0

The primary Phase II-III integrated database for this application included the following numbers of pediatric patients, aged 6-13 years.

OROS n=469
Ritalin n=300
Placebo n=276
[Total n=513]

The original NDA submission included data on 464 patients who had received OROS methylphenidate, and the safety updates included data on an additional 5 new patients for a total n=469. Altogether, 513 individual patients received study medication in these clinical trials. Because several studies (i.e., C-97-025, C-97-033, and C-98-003) used a crossover design, many patients were exposed to more than one treatment.

The demographic profile for these patients is shown below. As explained, the same patient may appear in different treatment groups.

Demographic Parameter	OROS (n=469)	Ritalin (n=300)	Placebo (n=276)
Aged 6-9 years (N)	275	169	167
Aged 10-13 years (N)	194	131	109
Median age, years	9	9	9
Male, %	83.4	84.3	84.4
Female, %	16.6	15.7	15.6
Caucasian, %	85.5	86.6	83.7
African-American, %	5.8	3.0	5.1
Hispanic, %	4.1	4.0	5.1
Other,%	4.1	5.4	5.4
Asian, %	0.6	1.0	0.7

The patient sample was predominantly male, reflecting the epidemiology of ADHD (according to DSM-IV, males with ADHD outnumber females with ADHD 4:1). With respect to ethnicity, the sample was predominantly caucasian.

Extent of exposure

In phase I type studies, the duration of exposure was generally not very long; 89% of healthy adult subjects received OROS methylphenidate for 3 days or less.

For trials involving pediatric patients, the dose and duration of exposure are displayed in the table below.

Number of Phase 2-3 patients exposed by duration of exposure

OROS daily dose	Total patients exposed*	Median duration of exposure, days	< 1 month	≥ 1 but <3 months	≥3 but <6 months	≥6 months
18 mg	278	25	146	70	23	39
36 mg	356	136	85	66	45	160
54 mg	229	147	46	49	29	105

*patients may be counted more than once
Source: ISS table 3.6, safety update

Expressed in terms of person-years, the exposure to OROS methylphenidate, Ritalin and placebo in the primary safety database is as follows. The imbalance reflects the open label continuation treatment with OROS methylphenidate; Ritalin and placebo were administered only during the double blind efficacy trials.

Treatment	n	Person-years
OROS	469	327.7
Ritalin	300	9.9
Placebo	276	7.6

The large number of patient years for OROS methylphenidate includes data from 432 patients entered into the long term open label study C-98-012. As of the 10/31/99 cutoff date, these subjects provided approximately 312 patient years of exposure to OROS methylphenidate.

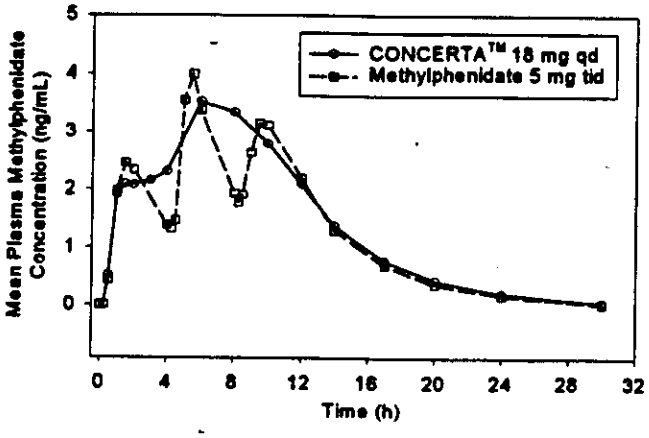
6.0 Pharmacokinetics

Methylphenidate is readily absorbed, and is eliminated primarily in the urine after metabolism to the inactive metabolite α–phenyl-piperidine acetic acid (PPA), also known as ritilinic acid. The AUC for the d-isomer is greater than for the l-isomer.

The following table, adapted from the sponsor, shows the pharmacokinetic parameters following OROS methylphenidate administration in adults.

Parameters	CONCERTA™ (18 mg qd) (n=36)	Methylphenidate (5 mg tid) (n=35)
C_{max} (ng/mL)	3.7	4.2
T_{max} (h)	6.8	6.5
AUC_{inf} (ng·h/mL)	41.8	38.0
$t_{½}$	3.5	3.0

The following is the plasma concentration-time curve obtained after administration of 18 mg OROS methylphenidate, with conventional methylphenidate 5 mg TID (every 4 hours) for comparison (adapted from sponsor, n=36 adult subjects).



7.1 Overview of studies pertinent to efficacy

Alza has proposed that the following three studies demonstrate efficacy of this drug product in the treatment of ADHD.

C-98-003 Double blind, randomized, single site, 3 way crossover trial;
OROS 18-54 mg/d
Ritalin IR 15-45 mg/d
Placebo
Each treatment x 1 wk
N=64 children with ADHD

C-97-025 Similar to C-98-003 above.
N=70 children with ADHD

C-98-005 Randomized, double blind, multisite, parallel group, 3 arm study;
OROS 18-54 mg/d
Ritalin IR 15-45 mg/d
placebo
duration 28 days
n=312 children with ADHD

The first two studies listed were single site crossover studies that were essentially identical in design; each treatment was administered for one week. The third study was a parallel group study with a treatment duration of 4 weeks. The two crossover studies employed a laboratory classroom setting for certain of the assessments, while there was no use of a laboratory classroom in the parallel group study. The results of these studies will be described.

A brief discussion of the sponsor's outcome measures is appropriate here. The Conners rating scales, in various forms, have been widely used in the past two decades for assessment of ADHD symptoms. The ratings are completed by the child's teacher and/or parents. The sponsor employed the IOWA (Inattention Overactivity with Aggression) Conners scale, completed by the child's teacher. This includes the following items, divided into the inattention/overactivity (IO) and the oppositional defiant (OD) subscales. Items are rated on a 0-3 scale. The sponsor selected the I/O subscale as the primary efficacy measure.

Inattention/Overactivity Subscale

1. Fidgeting
2. Hums and makes other odd noises
3. Excitable, impulsive
4. Inattention, easily distracted
5. Fails to finish things he/she starts (short attention span)

Oppositional/Defiant Subscale

1. Quarrelsome
2. Acts "smart"
3. Temper outbursts (explosive and unpredictable behavior)
4. Defiant
5. Uncooperative

To assess duration of effect, Alza employed a recently devised rating instrument known as SKAMP (for the originators, Swanson, Kotkin, Alger, M-Flynn and Pelham). This was administered throughout the day in the laboratory classroom. Drs. Swanson and Pelham were also clinical investigators for the OROS methylphenidate development program.

These are the individual items of the SKAMP:

1. Getting started on assignments for classroom periods
2. Sticking with tasks or activities for allotted time
3. Completing assigned work
4. Performing work accurately
5. Being careful and neat while writing or drawing
6. Interacting with others: separate ratings for interactions with children (eg, other students) and adults (eg, teacher or aide)
7. Remaining quiet according to classroom rules
8. Staying seated according to classroom rules
9. Complying with usual requests or directions of teachers
10. Following the rules established for the school

B1. Difficulty attending to an activity or discussion of the class

B2. Difficulty stopping and making transition to next period

Each item is rated on a 0-6 scale, with 6 representing the most symptomatic rating. Items 6, 7, 8, 9, and 10 are the deportment scale, and the combined attention scale (i.e., combining attention ratings for school work and for non-school work) includes items 1, 2, 3, 4, 5, B1 and B2.

The SKAMP is a recently developed instrument, and Wigal et al. first described its use to obtain multiple ratings within the same day (Psychopharm Bull 34(1):47-53, 1998).

The sponsor also employed the SNAP-IV, a questionnaire concerning ADHD behaviors completed by the parents and school teacher.

7.2 Summary of studies pertinent to efficacy

7.2.1 Study C-98-003

7.2.1.1 Investigators/ Sites

This study was conducted during September 1998 through January 1999 by James Swanson, PhD and Sharon B Wigal, PhD, at the University of California, Irvine.

7.2.1.2 Objective

The stated objective of this trial was to determine the safety and efficacy, including time course of effect, for OROS methylphenidate compared to immediate release Ritalin and placebo in ADHD patients.

7.2.1.3 Population

The protocol specified the following patient population: 63 children aged 6-12 years, male or female, receiving methylphenidate for ADHD. The diagnosis of ADHD was to be confirmed by interview with the parent and child, and a teacher SNAP-IV rating. Subjects needed to be methylphenidate responders and were not to be using doses in excess of 60 mg/d. ADHD was to be their primary diagnosis. Among the exclusion criteria were the following: gastrointestinal (GI) disorders such as narrowing of the GI tract, glaucoma, seizures, psychosis, Tourette's syndrome, significant learning disability, medical conditions in which methylphenidate use could be hazardous, and menarche for females.

7.2.1.4 Design

This was a single site, double blind, double dummy, randomized, 3 way, crossover study. The three treatments were OROS methylphenidate, commercial Ritalin TID, and placebo. Patients received a particular dose of double blind study medication based upon their previous dose of methylphenidate prior to the study. The sponsor's table showing the dose conversion is reproduced here.

Conversion from baseline methylphenidate dose to study dosage (reproduced from sponsor)

AM dose		Daily dose		Study Drug Dosage	
IR	**SR**	**Minimum**	**Maximum**	**OROS (QD)**	**Ritalin (TID)**
Low dose					
5-7.5	0	10	<25	18	5
0	20	20	25	18	5
Middle dose					
7.5	0	25	45	36	10
10	0	20	45	36	10
12.5	0	25	45	36	10
≤7.5	20	25	45	36	10
≤5	40	≥40	45	36	10
High dose					
12.5	0	>45	60	54	15
15-20	0	30	60	54	15
>7.5	20	>27.5	60	54	15
>5	40	>45	60	54	15
0	60	60	60	54	15

Patients received each of the three study treatments for 7 days at a time, with no washout in between. Days 7, 14 and 21 (the final days of each crossover period) were conducted in a laboratory classroom setting. Prior to the double blind portion of the study, all children attended a practice day at the laboratory classroom and were administered standard Ritalin treatment, with the dosage based upon their regular methylphenidate daily dose.

Screening procedures included diagnostic evaluation with DISC and SNAP-IV (see above) and physical exam, intelligence testing (WISC-III) and a practice visit to the laboratory classroom.

Outcome measures included the Teacher IOWA Conners scale from the child's community school teacher, the laboratory school SKAMP measure, the laboratory school teacher IOWA Conners scale, actigraphy monitors, parent/caregiver IOWA Conners scale, parent and teacher SNAP-IV, and other secondary measures.

Other parameters monitored during the study included plasma drug levels, clinical labortories, and vital signs. Topical anesthetic was employed to reduce the discomfort of venipuncture.

7.2.1.5 Analysis

The primary efficacy parameter was specified in the protocol to be the community school teacher IOWA Conners scale, Inattention/Overactivity subscale. The time course of the drug effect was to be assessed using the laboratory classroom SKAMP ratings, which were obtained periodically throughout the day. The protocol specified the primary efficacy population to be completers; i.e., all children having community teacher IOWA Conners scale scores for all 3 periods. The primary efficacy analysis was to be conducted with a mixed effects analysis of variance (ANOVA). The primary comparison was specified as OROS versus placebo. Secondary variables were to be analyzed with the sample of all randomized patients. In addition, the protocol allowed for an interim analysis for the purpose of planning future protocols; the study was not to be stopped on the basis of this analysis.

7.2.1.6 Results

Demographics

The sponsor's table showing the demographics of all randomized patients is reproduced below.

Demographics Summary (n=64)

Age (year) - n (%)	
6 - 9	33 (51.6%)
10 - 12	31 (48.4%)
Mean (SD)	9.2 (1.8)
Median	9
(Min, Max)	(6, 12)
Sex - n (%)	64 (100.0%)
Male	52 (81.3%)
Female	12 (18.8%)
Race - n (%)	64 (100.0%)
Caucasian	53 (82.8%)
Black	4 (6.3%)
Asian	2 (3.1%)
Hispanic	5 (7.8%)
Other	0

The majority of patients had combined type ADHD (83%), while 14% had predominantly inattentive type and 3% had predominantly hyperactive/impulsive type.

Patient disposition

Sixty four children were randomized after screening; the total number of children screened was not provided. Of these 64 children, one dropped out before receiving double blind treatment (parental decision). Another child dropped out because of a rash while on Ritalin during the study, and one child was dropped because of a protocol violation (received methylphenidate and clonidine outside the study). Thus, 61 patients completed the entire crossover sequence.

Dosing

The table below shows the numbers of patients assigned to each dosage level, based on their previous methylphenidate dose in the manner described above.

Study drug	N
18 mg OROS/ 5 mg Ritalin TID	10
36 mg OROS/10 mg Ritalin TID	34
54 mg OROS/15 mg RitalinTID	20

Approximately 65-70% of the patients in each dosage level received methylphenidate only on school days prior to the study.

Concomitant medications

The following numbers of patients used these types of medication during the study.

Drug	N
Analgesic	5
Antibacterial	1
Antihistamine	1
Antiasthmatic	1
Other	2

Thus, the vast majority of patients received no concomitant medications during the study.

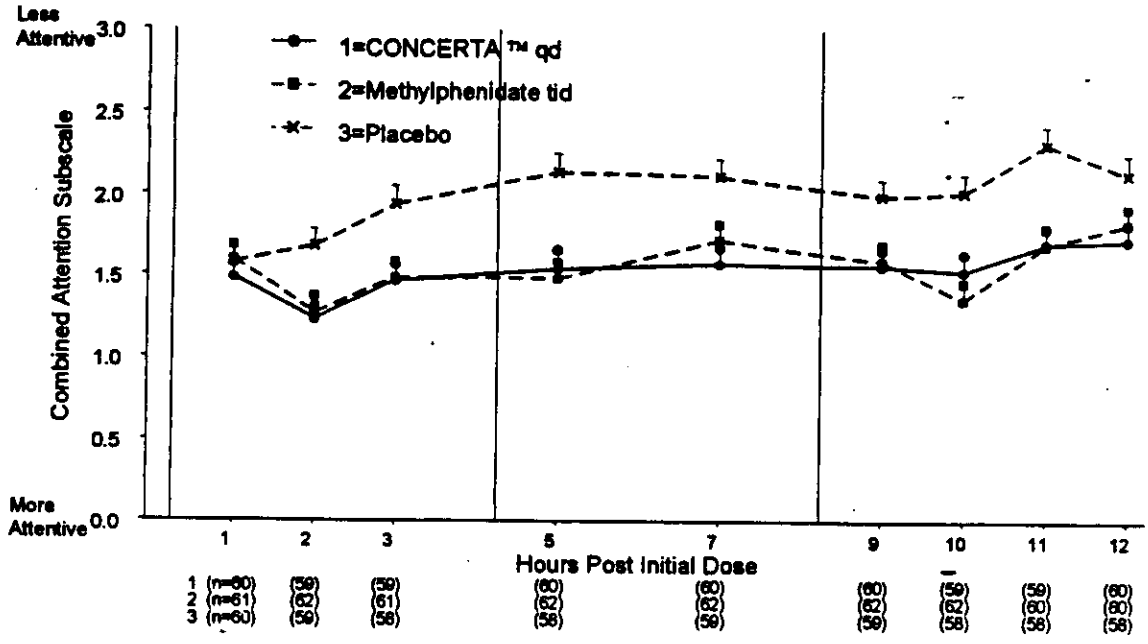
Efficacy measures

This table displays the results on the primary efficacy measure, the community teacher's IOWA Conners Inattention/Overactivity subscale (n=61)

Drug group	OROS	Ritalin TID	Placebo
Mean (SD)	6.5 (3.5)	6.9 (4.1)	11.6 (3.9)
p-value vs. pbo	<0.001	<0.001	-
p-value OROS vs.Ritalin = 0.3			

The first period scores were the highest on average, regardless of treatment.

On the secondary measure SKAMP, the sponsor's graph below depicts the results.



This graph depicts the results for the attention SKAMP items. Similarly, for the deportment subscale, both active drug treatments were also superior to placebo throughout the day.

One of the secondary outcome measures was actigraphy, which is of interest because it the data is obtained automatically and therefor objectively. Activity levels generally showed an effect of both drug treatments during structured tasks, but not during unstructured activity times, throughout the day.

7.2.1.7 Conclusions

This study provided evidence of efficacy of the drug product in children with ADHD, as rated by the community schoolteacher. The findings for the secondary outcome measures from the laboratory classroom setting also favored the drug product over placebo. Marketed Ritalin, the active control, was also effective.

7.2.2 Study C-97-025

7.2.2.1 Investigator/site

This study was a single site trial conducted by William E Pelham, Jr, PhD. The site was the State University of New York, at Buffalo.

7.2.2.2 Objective

The protocol-defined objective of this study was to compare the efficacy of OROS methylphenidate, Ritalin, and placebo, including assessment of the duration of effect.

7.2.2.3 Population

The study population specified in the protocol was essentially the same as for study C-98-003 described above. One minor difference was that glaucoma was not a specific exclusion criterion in this study. The sample size was identical (n=63). Screening procedures for subjects were specified in a separate protocol (C-97-006).

7.2.2.4 Design

This was a single site, double blind, double dummy, randomized, placebo controlled, crossover study. The treatments administered were OROS methylphenidate, Ritalin, and placebo, each for 1 week. The study design and the method of determining the dose of study medication were essentially the same as for study 98-003 described above.

7.2.2.5 Analysis

The analysis plan was essentially the same as for study 98-003.

7.2.2.6 Results

Demographics

Seventy patients were randomized in this trial. The sample was primarily male caucasian subjects with a median age of 9 years. The sponsor's table below summarizes the demographic characteristics of the sample.

Demographic characterisitcs:

Age (year) - n (%)	70 (100.0%)
6 - 9	41 (58.6%)
10 - 12	29 (41.4%)
Mean (SD)	9.1 (1.6)
Median	9
(Min, Max)	(6, 12)
Sex - n (%)	70 (100.0%)
Male	62 (88.6%)
Female	8 (11.4%)
Race - n (%)	70 (100.0%)
Caucasian	66 (94.3%)
Black	0
Asian	0
Hispanic	3 (4.3%)
Other	1 (1.4%)

Diagnostically, the sample was 76% combined type ADHD, 21% inattentive type, and 3% hyperactive-impulsive type.

Patient disposition

Eighty four subjects were screened for eligibility and 70 of these subjects were randomized. Of the 70 randomized subjects, 68 completed all three crossover periods and were included in the primary analysis. Two subjects were discontinued for protocol violations (subjects 29039 and 29067 received treatment with marketed Ritalin).

Dosing

Based on their pre-study methylphenidate treatment history, subjects were assigned to the following dose levels for study medication:

Study drug	N
18 mg OROS/ 5 mg Ritalin TID	17
36 mg OROS/10 mg Ritalin TID	39
54 mg OROS/15 mg RitalinTID	14

Concomitant medication

The following numbers of patients used these types of medication during the study, out of the total of 70 randomized subjects.

Drug	N
Analgesic	20
Antibacterial	10
Anti-inflammatory	4
Other ($n \leq 3$)	20

Efficacy measures

This table displays the results on the primary efficacy measure, the community teacher's IOWA Conners Inattention/Overactivity subscale (n=70, all randomized patients)

Drug group	OROS	Ritalin TID	Placebo
Mean (SD)	4.7 (3.3)	5.0 (3.7)	10.3 (4.2)
p-value vs. pbo	<0.001	<0.001	-
p-value OROS vs.Ritalin = 0.5			

Note that the sponsor presented the results using all randomized subjects rather than completers, but since the two groups differed in size by only n=2 it is unlikely that this impacts the results very much. The sponsor reported no significant sequence effects.

Below the sponsor's graph of the laboratory classroom SKAMP results for the attention subscale.

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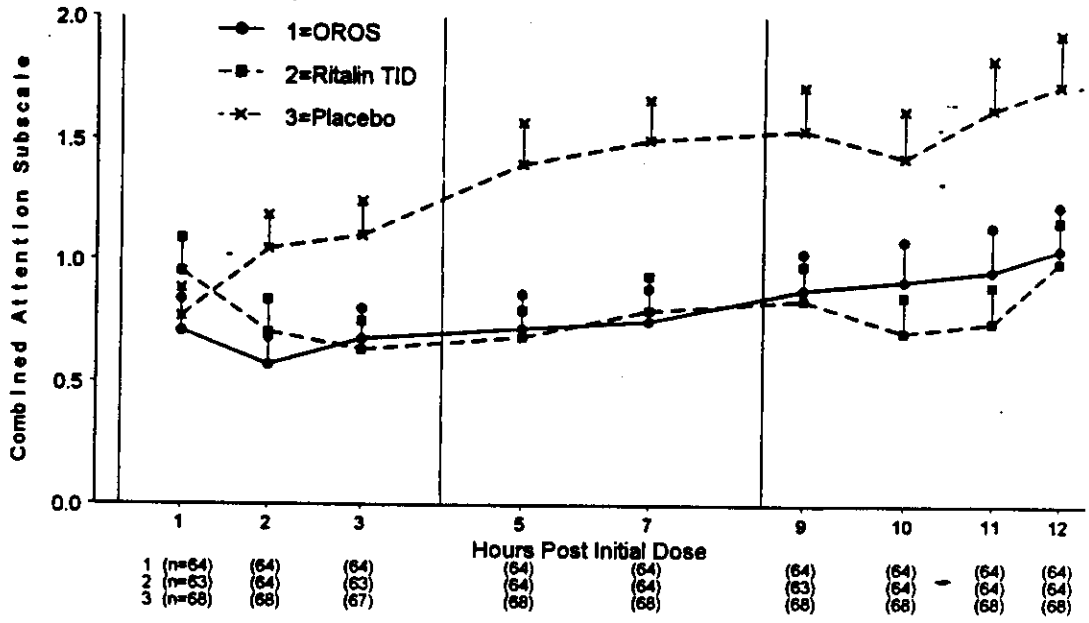

Note: Mean and mean plus standard error of mean shown

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Results on the deportment subscale were generally similar and favored both active treatments over placebo throughout the day.

7.2.2.7 Conclusions

This study provided evidence of the efficacy of the drug product in children with ADHD. As with the previous study, the primary outcome measure was the community teacher's rating. The secondary measures obtained in the laboratory classroom setting also favored the drug product over placebo.

7.2.3 Study C-98-005

7.2.3.1 Investigators/sites

Below is a list of the principal investigators and the 14 sites. In parentheses I have listed the number of patients enrolled by each site.

Howard Abikoff, Ph.D. NYU Medical Center, New York NY (13)
Marc Atkins, Ph.D. Univ. of Illinois at Chicago Neuropsychiatric Inst., Chicago IL (28)
Gerald August, Ph.D. Univ. of Minnesota Hospital and Clinics, Minneapolis MN (21)
J. Biederman, M.D. and T. Wilens, M.D. Mass. General Hosp., Boston MA (24)
Oscar Bukstein, M.D. Western Psychiatric Institute and Clinic, Pittsburgh PA (22)
C. Keith Conners, Ph.D. Duke Univ. Medical Center, Durham NC (14)
Larry Greenhill, M.D. New York State Psychiatric Inst., New York NY (10)
M. Manos, Ph.D. Univ. Hosp. of Cleveland (Case Western Reserve), Cleveland OH (30)
Keith McBurnett, Ph.D. Univ. of Chicago Dept. of Psychiatry, Chicago IL (27)

Donna Palumbo, Ph.D. Univ. of Rochester Strong Memorial Hosp., Rochester NY (28)
William Pelham, Jr., Ph.D. State Univ. of New York, Buffalo NY (27)
Mark Stein, Ph.D. Children's Hosp. Consultative Center, Fairfax VA (15)
James Swanson Ph.D. and Sharon Wigal Ph.D. Univ. of CA at Irivine, Irvine CA (26)
Mark Wolraich, M.D. Vanderbilt Univ. Medical Center, Nashville TN (27)

After the study concluded, but before the data were unblinded, Alza determined that there were data integrity concerns about the clinical data from Dr. Manos' site (designated site #3). Consequently, data from this site were included only for safety analyses. Dr. Manos enrolled 30 of the 312 subjects in this trial.

7.2.3.2 Objective

The objective of this study was to determine the safety and efficacy of OROS methylphenidate in comparison to placebo and marketed Ritalin immediate release.

7.2.3.3 Population

The protocol specified a sample size of up to 354 patients. Subjects were to be children aged 6-12 years, and were to have completed a screening procedure specified in a separate protocol (C-98-011). The screening protocol included a diagnostic interview with the child and caregiver, and a teacher rating on the SNAP-IV. Children were to have either previously received methylphenidate up to a dose of 60 mg/day or participated in Alza's study C-98-007, an open label study of OROS methylphenidate. Exclusion criteria included gastrointestinal disorders such as narrowing of the gastrointestinal tract, glaucoma, seizures, psychosis, Tourette's syndrome, depression, suicidality, and intolerance to methylphenidate. Nothing specific was mentioned in the protocol about the children having a diagnosis of ADHD, although this was the intention.

7.2.3.4 Design

This was a four week, randomized, double blind, double dummy, parallel group, placebo controlled trial. Patients were randomized to receive marketed Ritalin 5-15 mg TID, OROS methylphenidate 18-54 mg/day, or placebo. The assigned dosage was determined from the child's previous dosage of methylphenidate, as described for study C-98-003 above. Children who had been titrated to a dose of OROS methylphenidate in the open label study C-98-007 were similarly assigned to the corresponding dosage level. Efficacy assessments included weekly Conners teacher and parent rating scales, some other secondary outcome scales, and baseline and end of study SNAP-IV ratings. Vital signs and adverse effects were monitored. There was no laboratory classroom assessment in this trial.

There were two protocol amendments. One provided for exclusion of Dr. Manos' data because of data integrity concerns, and the other provided for minor clarifications of various items in the protocol.

The sponsor's summary of the study schedule is reproduced below.

Study C-98-005 schedule of events (reproduced from sponsor)

ASSESSMENTS										
Day:	Day −1 or earlier	-1	0	1, 8, 15, 22	2, 9, 16, 23	3, 10, 17, 24	4, 11, 18, 25	-5, 12, 19, 26	6, 13, 20	27
Activity		FRI	SAT	SUN	MON	TUES	WED	THUR	FRI	FRI
Informed Consent	X									
Dispense Study Drug			X							
Study Drug Administration				X	X	X	X	X	X	X
Community school teacher (CS) global assessment										X
CS Teacher IOWA Conners[e]		X							X	X
CS Teacher peer interaction items[e], SNAP-IV[e]		X								X
Parent/caregiver IOWA Conners[e]		X							X	X
Parent/caregiver global assessment, SNAP-IV[e], Home Situations Questionnaire		X								X
Investigator CGI										
Parent Satisfaction Questionnaire										
Vital Signs	X		X							
Sleep, tic evaluation			X							
Appetite evaluation										
Physical Exam & Laboratory Tests	X[a]									
Adverse Event Assessment										

[a] Not required if patient completed ALZA protocol C-98-007 within 4 weeks of randomization.
[b] Required for patients who prematurely terminated from C-98-005 or who did not enroll into ALZA protocol C-98-012.
[c] In practice could be done on Days 13 or 14.
[d] In practice could be done on Days 27 or 28.
[e] The SNAP-IV ratings from C-98-011 were used as the baseline ratings in this study.

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7.2.3.5 Analysis

The protocol specified the Day 27 IOWA Conners Teacher Rating Scale (Inattention/Overactivity subscale) by the Community School Teacher as the primary variable. The statistical method specified in the protocol was ANOVA with a protected LSD approach; pairwise comparisons were not to be made unless the overall p value was 0.1 or lower. ANCOVA models were to be used, if needed, to correct for imbalances in baseline characteristics. Note that the observed score, and not the change from baseline, was the specified variable. The specified sample was the set of all randomized patients with community teacher Conners rating scale assessments.

7.2.3.6 Results

Demographics

A total of 312 patients were enrolled, 102 of which had participated in the open label trial C-98-007. Excluding the 30 patients from Site 3 (Dr. Manos), the following table, adapted from the sponsor's submission, displays the demographic characteristics of the sample.

	Treatment Group		
	OROS (methylphenidate HCl) (n=95)	Ritalin TID (n=97)	Placebo (n=90)
Age (years) - n(%)	95 (100.0%)	97 (100.0%)	90 (100.0%)
5 - 9	63 (66.3%)	51 (52.6%)	57 (63.3%)
10 - 13	32 (33.7%)	46 (47.4%)	33 (36.7%)
Mean (SD)	8.8 (1.7)	9.1 (1.9)	8.9 (1.8)
Median	9.0	9.0	8.5
(Min, Max)	(5, 12)	(6, 13)	(6, 13)
Sex - n(%)	95 (100.0%)	97 (100.0%)	90 (100.0%)
Male	74 (77.9%)	84 (86.6%)	75 (83.3%)
Female	21 (22.1%)	13 (13.4%)	15 (16.7%)
Race - n(%)	95 (100.0%)	97 (100.0%)	90 (100.0%)
Caucasian	79 (83.2%)	87 (89.7%)	72 (80.0%)
Black	7 (7.4%)	4 (4.1%)	10 (11.1%)
Asian	0	1 (1.0%)	0
Hispanic	4 (4.2%)	(2.1%)	4 (4.4%)
Other	5 (5.3%)	3 (3.1%)	4 (4.4%)
Prior ADHD Therapy[a] - n(%)	95 (100.0%)	97 (100.0%)	90 (100.0%)
None	20 (21.1%)	18 (18.6%)	19 (21.1%)
No Drug	3 (3.2%)	9 (9.3%)	6 (6.7%)
Non-methylphenidate	3 (3.2%)	8 (8.2%)	5 (5.6%)
Methylphenidate	69 (72.6%)	62 (63.9%)	60 (66.7%)

Note that one patient was aged 5 years and two patients were aged 13 years at enrollment, contrary to the protocol.

As noted above, whether a particular child received the low, middle, or high dosage of double blind study medication was determined from the child's previous methylphenidate treatment. Of the 282 subjects, 90 were assigned to the low dosage of study medication, 122 to the middle dose, and 70 to the high dosage.

The diagnostic subtypes of ADHD for the subjects are shown in the sponsor's table, reproduced below.

Diagnostic Criteria - ADHD Diagnosis and Comorbidities: All Randomized Patients (Site 3 Excluded)

	Treatment Group		
	OROS methylphenidate HCl (n=95)	Ritalin TID (n=97)	Placebo Patients (n=90)
ADHD diagnosis - n(%)			
Combined	74 (77.9%)	64 (66.0%)	69 (76.7%)
Predominantly inattentive	16 (16.8%)	27 (27.8%)	12 (13.3%)
Predominantly hyperactive -impulsive	5 (5.3%)	6 (6.2%)	9 (10.0%)
Comorbidities			
Oppositonal Defiant Disorder	35 (36.8%)	40 (41.2%)	43 (47.8%)
Conduct Disorder	9 (9.5%)	9 (9.3%)	14 (15.6%)
Tics Disorder	6 (6.3%)	5 (5.2%)	4 (4.4%)
Anxiety Disorder	0	0	4 (4.4%)
Depression	0	1 (1.0%)	1 (1.1%)

(A patient may be reported in more than one comorbidity category.)

Patient disposition

A total of 312 patients were randomized. Five patients were randomized but did not receive study medication. Thirty patients from Dr. Manos' site were excluded from the sample. Also, patients with ratings more than 10 days after receiving study medication were excluded from the efficacy analyses for that scale; this resulted in dropping one patient from the primary outcome variable analysis. and several patients from various secondary outcome variable analyses. The following patients were excluded from the primary efficacy analysis, for the reasons shown.

Randomized but not treated (n=5)
Dr. Manos' site (n=30)
Teacher ratings obtained more than 10 days after last treatment (n=1)

Similarly, patients with ratings on the secondary outcome variables that were obtained more than 10 days after study medication were excluded from those analyses.

The following table shows the patient disposition for this trial. The numbers shown are the numbers of patients in each catgegory.

Study C98005: Patient Disposition

Treatment group	OROS	Ritalin	Placebo
Randomized	95	97	90
Treated	94	94	89
Completed	79	81	46
Reason for d/c			
Adverse event	1	1	1
Protocol violation	0	1	1
Noncompliance	1	1	1
Lost to follow up	1	0	0
Lack of efficacy	11	10	38
Other	1	0	2

The following table, adapted from the sponsor's submission, displays the patient completion rates by week. Note that the lowest completion percentage was in the placebo group.

Number (%) of Patients Who Completed Study Medication by week

	Oros	Ritalin	Placebo
1 Week	91 (95.8%)	88 (90.7%)	69 (76.7%)
2 Weeks	88 (92.6%)	82 (84.5%)	52 (57.8%)
3 Weeks	83 (87.4%)	81 (83.5%)	47 (52.2%)
4 Weeks	79 (83.2%)	81 (83.5%)	46 (51.1%)

Dosing

The numbers of patients assigned to low, middle, or high doses, based on their pre-study methylphenidate treatment history, are listed below.

Numbers of patients
OROS (n=95)
Low dose (18 mg/d) 31
Middle dose (36 mg/d) 41
High dose (54 mg/d) 23

Ritalin (n=97)
Low dose (5 mg TID) 30
Middle dose (10 mg TID) 41
High dose (15 mg TID) 26

Placebo (n=90)
Low dose 29
Middle dose 40
High dose 21

In all three treatment groups, the middle dose assignment was the most common.

Concomitant medication

Below is a list of the types of concomitant medications received by 5% or more of patients in any treatment group during the trial. The sponsor did not provide a tabulation by specific drug.

Percentage of patients receiving

Concomitant Drug class	OROS	Ritalin	Placebo
Anti-infectives	9.6	6.7	7.1
Analgesics	8.7	11.5	9.2
Anti-inflammatory	3.8	6.7	2.0
Vitamins	4.8	4.8	6.1
Antihistamines	6.7	5.8	7.1
Asthma drugs	3.8	5.8	6.1
Cough/cold drugs	2.9	8.7	3.1

There did not appear to be significant discrepancies between treatment groups for concomitant medications.

Efficacy measures

For the primary outcome measure, the Teacher's IOWA Conners Inattention/Overactivity scale, the following were the results. The mean score at baseline was 9.7, 9.9 and 10.3 for OROS, Ritalin and placebo, respectively; these were not statistically significantly different. At endpoint (week 4 LOCF), the mean scores were 6.0, 6.4 and 9.8 for OROS, Ritalin and placebo, respectively; the p-value for comparison of both active drugs to placebo was <0.001. A graphic display of the results is shown below, by week, reproduced from Alza's study report. All Ritalin-placebo and OROS methylphenidate-placebo contrasts for each week were statistically significant.

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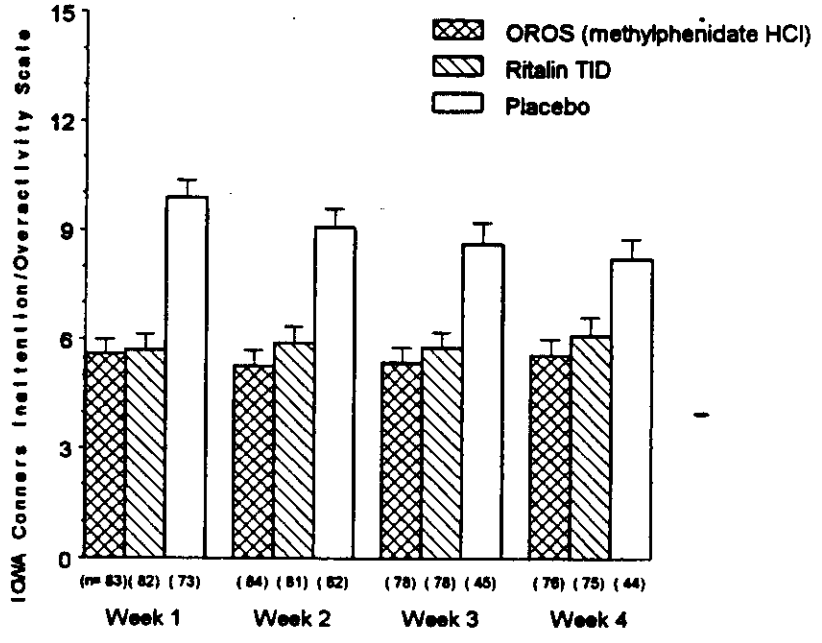
FIGURE E
Community School Teacher IOWA Conners -
Mean (SEM) of Inattention/Overactivity Subscale Over Time
(Site 3 Excluded)



Observed Cases by Week

Source: C98005\STAT\FINAL\FIGPGM\PLTIOOT2.SAS SBH (26MAY99 15:16) E

With respect to secondary outcome measures, the mean scores for the abbreviated Conners scale were 9.6, 9.9 and 15.9 for OROS, Ritalin, and placebo, respectively; these differences were statistically significant. Results on the other secondary outcome measures generally favored the two active treatments over placebo.

7.2.3.7 Conclusions

The results from this study support the efficacy of the drug product in the treatment of children with ADHD. Marketed Ritalin was also effective.

8.0 Safety findings

8.1 Methods

The principle source of data for the safety review was the sponsor's integrated summary of safety (ISS), which Alza updated twice, after 4 months and 7 months. Safety data from Dr. Manos' site was included in the primary safety database by the sponsor, although data from this site was excluded from the efficacy analyses because of data integrity concerns. The sponsor chose to analyze safety data from the Phase I studies in healthy adult volunteers separately from the primary safety database, which comprises the pediatric patients with ADHD. The sponsor used COSTART terms for adverse events.

In December 1999 Alza submitted a safety update for this application. The cutoff date for the safety update data set was 8/3/99, and the update included additional data from an ongoing long term safety study C-98-012. Alza also took the opportunity to use the safety update to correct various errors in the original submission. In February 2000 Alza submitted a 7 month safety update, including safety data from ongoing studies through October 31, 1999. All the additional clinical trial data in the 7month update came from open label treatment with OROS methylphenidate; no additional controlled trial data was submitted. Additionally, the sponsor deleted safety data for one subject (#19121) when it was discovered that the subject had not received any study medication.

8.2 Deaths

There were no deaths in these clinical studies.

8.3 Assessment of dropouts

8.3.1 Overall pattern of dropouts

The following table, adapted from the sponsor's 7 month safety update, displays the overall pattern of dropouts from the clinical studies with patients. The data below are derived from the termination section of the case report forms. Dropouts for adverse events apparently could also be noted in the adverse event section of the case report form, and there were some discrepancies between the two listings.

Treatment Group	OROS	Ritalin	Placebo
Number (%) of Patients	469 (100.0%)	300 (100.0%)	276 (100.0%)
Number (%) Completing	312 (66.5%)	284 (94.7%)	225 (81.5%)
Number (%) of Dropouts by Termination reason			
Adverse Events	29 (6.2%)	1 (0.3%)	1 (0.4%)
Protocol Violation	3 (0.6%)	2 (0.7%)	2 (0.7%)
Noncompliance	14 (3.0%)	1 (0.3%)	3 (1.1%)
Personal Reason	10 (2.1%)	0	0
Lost to Follow-up	15 (3.2%)	0	0
Site Terminated (site 3)	20 (4.3%)	0	0
Lack of Efficacy	42 (9.0%)	10 (3.3%)	41 (14.9%)
Onset of Menarche	6 (1.3%)	0	0
Other	22 (4.7%)	2 (0.7%)	4 (1.4%)

Patients may be counted in more than one treatment group for cross-over studies

As might be expected, lack of efficacy was a more frequent reason for discontinuation in the placebo group, while adverse events were more frequently associated with discontinuation in the OROS group, although not in the Ritalin group. It should be recalled that the table above displays the data for all clinical studies, so the OROS methylphenidate figures include a mixture of double blind and open label experience, while the control treatments show only data from double blind studies. Alza reported finding inconsistencies in the case report forms for many of these dropouts, with respect to dates and reasons for dropout (ISS table 5.4B).

8.3.2 Adverse Events Associated with Dropout

Adverse events associated with discontinuation (table adapted from sponsor's Table 5.3 in 7 month safety update) are depicted below. These data are derived from the adverse event information recorded on the case report forms, in contrast to the description noted under "reason for termination," so there are some discrepancies with the table above.

Treatment Group	OROS n=469	Ritalin n=300	Placebo n=276
Number (%) of Patients Who Discontinued Due to Adverse Events	30 (6.4%)	2 (0.7%)	4 (1.4%)
Body as a Whole			
Aggravation reaction	3 (0.6%)	1 (0.3%)	2 (0.7%)
Headache	2 (0.4%)	0	1 (0.4%)
Abdominal pain	1 (0.2%)	0	0
Reaction unevaluable ("skin picking")	1 (0.2%)	0	0
Cardiovascular system			
Hypertension	1 (0.2%)	0	0
Digestive System			
Anorexia	4 (0.9%)	0	1 (0.4%)
Nausea	1 (0.2%)	0	0
Nervous System			
Twitching	8 (1.7%)	0	1 (0.4%)
Insomnia	4 (0.9%)	0	2 (0.7%)
Hostility	3 (0.6%)	0	0
Somnolence	2 (0.4%)	0	0
Abnormal dreams	1(0.2%)	0	0
Depression	1 (0.2%)	0	0
Emotional lability	1 (0.2%)	1 (0.3%)	0
Hallucinations	1 (0.2%)	0	0

Note: Data were collected from Clinical studies C-96-051, C-97-025, C-97-033, C-98-003, C-98-005, C-98-007,and C-98-012. Patients may be counted in more than one treatment group for cross-over studies C-97-025, C-97-033, and C-98-003.

Overall, twitching was the single adverse event that resulted in discontinuation for more than 1% of treated patients. With respect to "twitching," this is indeed the correct COSTART to refer to tics and Tourette's Syndrome (although, in my opinion, it is an imprecise use of the word "twitching"). Review of the cases of dropout for "twitching" revealed that all 8 OROS methylphenidate, and the one placebo patient, discontinued for tics. In controlled trials, only 2 subjects discontinued OROS methylphenidate because of adverse events (for depression in one subject and insomnia plus headache in the second subject). The remainder of the OROS methylphenidate adverse dropouts were during open label treatment (study C98012). Only one of the adverse dropouts involved an adverse event considered serious: OROS methylphenidate subject 19192 who required hospitalization for hostility (aggressive behaviors).

In addition to the above, subject 19001 in the clinical pharmacology study C97033 discontinued OROS methylphenidate for high blood pressure (up to 137 mmHg systolic)

but for some reason this was not considered an adverse event and is not listed as such above.

8.4 Serious adverse events

Eight serious adverse events occurred in this clinical development program, all associated with OROS methylphenidate open label treatment under protocol C-98-012. Below is a list of these events.

Patient	Serious Adverse event
19105 10 year old boy	Severe headache, evaluated in emergency room to rule out meningitis
19192 12 year old boy	Hospitalized for aggressive behavior (threatening family members with a knife)
29121 10 year old boy	Hospitalized for viral infection
169005 7 year old boy	Leg fracture sustained in motor vehicle accident
39011 9 year old boy	Hospitalization for viral meningitis
169025 8 year old boy	Tonsillectomy and adenoidectomy
169024 13 year old boy	Tonsillectomy and adenoidectomy
19213 10 year old boy	Hospitalization for tracheitis

In addition, the sponsor noted two adverse events in subjects receiving the OROS product which were considered significant, but did not meet the exact criteria for "serious" events.

119014 9 year old boy	Onset of severe motor and vocal tics, including coprolalia, which have persisted after stopping OROS methylphenidate
19217 8 year old boy	Auditory hallucinations, resolved after medication discontinued

There were no serious adverse events in clinical pharmacology studies involving healthy volunteers.

There was one serious adverse event occurring in the open label study C98012 after the cutoff date of 10/31/99: new onset Type 1 Diabetes Mellitus, in subject 19047, a 14 year old boy.

In my opinion, of the adverse events described above, auditory hallucinations and tic disorder could be causally related to methylphenidate exposure, and in fact psychosis and Tourette's syndrome are noted in the labeling for Ritalin. I would not assume that the OROS formulation was a factor.

8.5 Other safety findings

8.5.1 Adverse event incidence

The placebo controlled trials allow comparison of adverse event incidences between OROS methylphenidate and placebo treated subjects. However, it should be recalled that all of the subjects in these trials had already been receiving methylphenidate, which limits the external validity of these findings for the general population of ADHD patients.

It may be useful to consider adverse event incidences based on pooling the data from the three placebo controlled trials. Alza emphasized analysis of adverse events attributed to the drug by the investigator, but in the table below I show the total for all adverse events regardless of the investigator's opinion about causality. This approach combines data from studies of different design (crossover and parallel group) and involving different lengths of treatment (1 week versus 4 weeks), which may not be ideal, but it does provide a larger sample size than considering individual studies separately.

ADVERSE EVENTS IN CONTROLLED STUDIES C-97-025, C-98-003, C-98-005 (% of patients experiencing the event by treatment group. Only events with an incidence of at least 1% for OROS are shown.)

ADVERSE EVENT	OROS (n=234)	Placebo (n=238)	Ritalin (n=236)
Headache	12.0	14.0	10.6
Abdominal pain	8.5	4.8	10.2
Fever	1.7	1.3	0.4
Aggravation reaction	1.3	1.3	1.3
Vomiting	3.0	2.6	2.5
Anorexia	2.1	0.4	1.7
Dizziness	2.1	0	0.4
Insomnia	2.1	1.8	2.1
Upper resp. tract infection	4.7	3.5	4.7
Cough increased	2.6	1.3	3.8
Pharyngitis	2.1	1.8	2.5
Sinusitis	1.3	0.4	0.4

To define the common and drug related adverse events, the following criteria are often used: relative risk (versus placebo) of at least 2, and absolute risk of at least 5 per 100. Applying these criteria, there were no adverse events considered common and drug related.

It may be more useful to examine the adverse events from the parallel group study C-98-005 separately. Recall that in this trial, subjects were treated with the same medication for 4 weeks. The table below displays the adverse event incidences.

ADVERSE EVENTS IN CONTROLLED STUDY C-98-005 (% of patients experiencing the event by treatment group. Only events with an incidence of greater than 1% for OROS are shown.)

ADVERSE EVENT	OROS (n=106)	Placebo (n=99)	Ritalin (n=107)
Headache	14.4	10.2	5.8
Abdominal pain	6.7	1.0	5.8
Aggravation reaction	1.9	2.0	1.9
Vomiting	3.8	3.1	1.9
Anorexia	3.8	0	0
Dizziness	1.9	0	0
Insomnia	3.8	1.0	1.0
Upper resp. tract infection	7.7	5.1	6.7
Cough increased	3.8	2.0	7.7
Pharyngitis	3.8	3.1	3.8
Sinusitis	2.9	0	1.0

Applying the same criteria for common and drug related adverse events, from the table above the event "abdominal pain" meets the criteria.

With respect to reported adverse events, if one were to hypothesize that removing children from methylphenidate treatment created withdrawal-related adverse reactions, then one might expect such withdrawal induced adverse events to be more frequent in the placebo group than the drug treated groups. From these data, I found no obvious pattern of adverse events in the placebo group that would suggest withdrawal reactions.

8.5.2 Laboratory findings

Despite the provision in the protocol for end of treatment clinical laboratories in the parallel group study C-98-005, these were obtained on only five subjects. In the crossover study C-98-003 and C-97-025 no on-treatment clinical laboratories were obtained. The absence of laboratory tests was noted by the Division of Scientific Investigations inspector who visited Dr. Swanson's site (please refer to the letter from DSI to Drs. Swanson and Wigal dated 1/27/00). Thus there is no meaningful data on the effect of this drug product on clinical laboratory parameters. Among the few patients on whom laboratories were obtained, there were apparently no significant abnormalities requiring discontinuation.

8.5.3 Vital signs and weight

In controlled clinical trials, 224 OROS methylphenidate treated subjects had vital sign measurements recorded, along with approximately equal numbers of subjects who received Ritalin or placebo. The sponsor tabulated the number of patients with blood pressure or pulse on treatment that exceeded the 95% percentile for age and sex. This approach was necessary because the normal range for these vital signs varies with age and gender, so a single criterion value to define abnormality would be imprecise.

The table below shows the percentage of patients in each treatment group having the vital sign value of interest. I revised the sponsor's calculations slightly to include only patients who had blood pressure measured on treatment in the denominator.

Vital sign parameter	OROS (n=219)	Ritalin (n=218)	Placebo (n=211)
Sys. BP > 95%ile	10.5%	11.9%	9.9%
Dias. BP > 95%ile	1.8%	2.3%	2.4%
Pulse > 95%ile	"no significant treatment effects;" no analysis provided		

Because this method may introduce "noise" in that any patient having a single vital sign measurement exceeding the 95th percentile is counted, it may be more useful to consider the vital sign data obtained throughout the day in the laboratory classroom studies. The sponsor chose to display these data graphically. There appeared to be increases of several mmHg for both diastolic and systolic BP with both active treatments versus placebo, in the crossover studies C97025 and C98003. Similarly, pulse increased with the active drug treatments by several beats per minute. The sponsor's graphs for one study (C98003) are appended to this review.

Vital signs were obtained at 6 month intervals in the open label extension study C98012, but I will not emphasize these data in this review since they are uncontrolled.

Two subjects discontinued OROS methylphenidate for hypertension (although this was counted as an adverse event in only one of the cases). Subject 159028 (a 10 year old boy in the open label extension study C98012) had blood pressure as high as 148/73 mmHg, and an 11 year old boy (subject 19001) in the clinical pharmacology study C97033 discontinued for blood pressure up to 137 mmHg systolic.

With respect to weight, the parallel group study C-98-005 would have provided the most meaningful data on short term weight changes, and it had the advantage of a placebo control group. However, post study physical exams (which were to have included weight) were performed on only 9 subjects in that trial, so no meaningful data on weight was obtained.

In sum, it appears that OROS methylphenidate increases blood pressure and pulse, consistent with the known effects of methylphenidate. This observation has implications for its use in patients with cardiovascular disease. This might be of particular importance if the product is widely used by adults. This application may afford an opportunity to re-examine the current methylphenidate labeling with respect to the existing warning about hypertension.

8.5.4 Electrocardiograms

No electrocardiograms were obtained in any of the pivotal trials.

8.5.5 Special topics

Alza specifically investigated three adverse reactions often attributed to methylphenidate: insomnia, loss of appetite, and tics.

Adverse effects on sleep

The investigators collected data on quality of sleep for the subjects in the trials. The sponsor's table below shows the data for the three placebo controlled trials combined.

Quality of Sleep (by worst report during trial):
Patients Treated in Controlled Studies

	OROS (methylphenidate HCl) (n=234)	Ritalin TID (n=236)	Placebo (n=228)
Sleep - n(%)	233 (100.0%)	232 (100.0%)	223 (100.0%)
Poor	27 (11.6%)	16 (6.9%)	19 (8.5%)
Fair	61 (26.2%)	53 (22.8%)	33 (14.8%)
Good	112 (48.1%)	130 (56.0%)	132 (59.2%)
Excellent	33 (14.2%)	33 (14.2%)	39 (17.5%)

Although the above table mixes data from 1 parallel and 2 crossover studies, it nonetheless appears to be consistent with a detrimental effect of OROS methylphenidate on sleep, to a greater degree than with conventional marketed Ritalin. (The sponsor did not perform statistical testing on these pooled data).

Decreased appetite

Below is the sponsor's pooled analysis of appetite effects from the three controlled trials. As with sleep, the "worst" ratings on treatment were used in this analysis.

Assessments of Appetite:
Patients Treated in Controlled Studies

	OROS (methylphenidate HCl)	Ritalin TID	Placebo
Appetite - n(%)	233 (100.0%)	232 (100.0%)	222 (100.0%)
Less than usual	51 (21.9%)	49 (21.1%)	19 (8.6%)
Usual amount	165 (70.8%)	164 (70.7%)	124 (55.9%)
More than usual amount	17 (7.3%)	19 (8.2%)	79 (35.6%)

It appears that both OROS and marketed methylphenidate reduce appetite. One may speculate that the "more than ususal amount" of appetite among the placebo patients reflects washout of methylphenidate during placebo treatment.

Tics

The sponsor collected reports of tics from parents or caregivers, including information on whether any reported tics were of new onset during the trial. The overall incidence of tics reported during controlled trial treatment was as follows.

OROS methylphenidate	10/233 (4.3%)
Ritalin	5/230 (2.2%)
Placebo	10/223 (4.4%)

For the patients enumerated above, tics were designated as new onset in three of the ten placebo patients, two of the five Ritalin patients, and none of the ten OROS methylphenidate patients with tics.

These data do not indicate a clear association of methylphenidate with tics. However, it should be recalled that the exposure to medication was of short duration in these trials, and that none of the subjects were naïve to methylphenidate treatment. Thus these data are of limited inferential value with respect to the question of treatment emergent tics. Alza points out that there is a certain level of comorbidity between tic disorders and ADHD.

In the long term open label study C-98-012, 432 patients were entered, and of these, 34 experienced new onset tics during the trial (Table 11.5, 7 month safety update). It might be of interest to calculate the cumulative probability of developing tics over the course of 12 months of treatment, and we have asked the sponsor to do so. Of course, there is no control group for comparison.

8.5.6 Withdrawal reactions and abuse potential

Please refer to the consultation by Dr. Michael Klein of HFD-170 regarding abuse potential. Alza has argued that the drug substance is relatively difficult to extract from the OROS tablet for the purpose of abuse by injection or insufflation. If a small child were to chew on the tablet it is likely that only the outer coat would be released.

Alza has not asked for a change in scheduling, so the OROS methylphenidate product would retain the Schedule II classification that other methylphenidate drug products share.

8.5.7 Human reproduction data

There is nothing relevant to human reproduction in these clinical data.

8.5.8 Overdosage experience

In the original NDA submission, the sponsor reported that six children had received a double dose of OROS methylphenidate, presumably by accident, and had no untoward sequelae.

8.5.9 Literature

As Alza has outlined in their submission, there is an extensive literature on methylphenidate's safety and efficacy. A summary of this literature, which spans roughly 40 years, would be beyond the scope of this review. I believe it is reasonable to assume that the labeling for Ritalin adequately reflects the existing clinical data.

8.5.10 Experience with the OROS formulation for other drug substances

Alza provided a summary of experience with other OROS formulations, with respect to reports of gastrointestinal obstruction resulting from the fact that the remnant of the tablet is insoluble. The greatest number of reports of obstruction and bezoar formation have apparently been associated with Procardia XL (nifedipine). For Procardia XL,

during the first 7 months of marketing the reporting rate for gastrointestinal obstruction was [redacted] prescriptions, with prescriptions averaging 34 tablets. Assuming one tablet per day, this yields a reporting rate of [redacted] person years. Alza states that the Procardia XL labeling was changed to advise caution for patients with gastrointestinal tract narrowing, and that the reporting rate declined subsequently. However, reporting rates generally tend to be higher for new products and decline with time, so it is difficult to judge the true impact of the labeling change.

[redacted]

R.,

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For the product Volmax (salbutamol), Alza states that there have only been two reports of intestinal obstruction, representing a reporting rate of slightly less [redacted] person years worldwide.

[redacted]

In a fax dated 7/12/99, Alza provided the tablet dimensions for OROS methylphenidate in comparison to other marketed OROS products. The 18 mg strength is a caplet 0.21 x 0.47 inches and the 36 mg strength is a caplet 0.27 x 0.59 inches. For comparison, Procardia XL 30 mg is a round tablet 0.34 inches in diameter and 0.18 inches thick.

GI irritation studies

[redacted]

mg/kg daily for 30 days. The sponsor reported no histopathologic evidence of GI lesions in the treated dogs.

Consultation from the Division of Gastrointestinal and Coagulation Drug Products

Dr. Joseph of HFD-180 provided consultation regarding the issue of adverse gastrointestinal reactions with this OROS product. Please refer to his consultation for details. He noted that the dimensions of the OROS methylphenidate product will make it among the largest such products ever marketed, and he recommended stronger labeling than the sponsor's prosposal (including contraindicating this product in conditions that predispose to gastrointestinal obstruction). I concur with his recommendations.

8.6 Adequacy of patient exposure and assessments

The database for this application can be considered sufficient given that methylphenidate has a long marketing history for this indication. The failure to collect safety monitoring data such as clinical laboratories and weights is unfortunate, and would be a far more serious deficiency if methylphenidate were a new melecular entity.

9.0 Conclusions

Efficacy

OROS methylphenidate is clearly effective in the treatment of ADHD when administered once daily. The question of what to conclude about the duration of its effect is somewhat more problematic. In the laboratory classroom setting, superiority of OROS methylphenidate over placebo was observed on the SKAMP results over 12 hours. However, what is not known is whether the SKAMP is as sensitive at measuring the offset of efficacy as it is in measuring the onset of effect. The laboratory classroom trials did not include a treatment arm with a shorter duration of effect (such as immediate release Ritalin in a single dose) to provide assay sensitivity. Accordingly, I would favor allowing the sponsor to claim efficacy when administered once a day, but not to claim a duration of effect of 12 hours or that the duration is equal to methylphenidate administered TID.

Safety

There were no safety findings that would preclude marketing of this product, in my opinion. In reaching this conclusion I am, of course, relying not only upon the data submitted in this application but also upon the substantial experience with the drug substance, methylphenidate. On balance, there were only minor differences in the adverse event profile for this formulation compared to that of conventional methylphenidate.

The greatest safety concern, in my opinion, is one that is at present only theoretical, and that is the potential for gastrointestinal reactions such as obstruction and bezoar formation. There were no such events among the patients who received this product in clinical trials. However, the reasons to be concerned about the potential for such events include the relatively large size of these tablets and their expected use in the pediatric population. We have received advice on this issue from HFD-180.

Labeling

I have the following comments regarding the sponsor's proposed labeling.

1. The clinical pharmacology section should indicate which data are from adults and which are from pediatric patients.

2. Under Clinical Studies, it is questionable whether Concerta should be described as having comparable efficacy to methylphenidate administered TID. Also, the statement that efficacy was maintained in the open label study is also questionable. The description of secondary outcome results should be curtailed, to be consistent with our usual policy on reporting secondary outcome measures in labeling.

3. The Warnings section should have separate headings for each topic; i.e., hypertension, Tourette's syndrome, et al. should be separated. A similar format change may be appropriate for the Ritalin label.

4. The labeling for gastrointestinal complications associated with OROS products should be strengthened (please refer to the consultation from the HFD-180).

5. The labeling includes a non-specific description of adverse events occurring with concomitant clonidine. While this is factual, no corresponding description has been added to the Ritalin labeling thus far.

[redacted] and will, of

7. There is no table of adverse event incidences in the Ritalin labeling. For this product, I recommend that the Adverse Event table (Table 2) not be limited to those events deemed "probably or possibly related." Also, I believe that some discussion of the fact that the subjects were not naïve to methylphenidate treatment when they entered the trials should be included.

8. The Overdosage section appropriately notes the risk of extended release of the drug substance after an overdose.

10.0 Recommendations

I recommend an "approvable" action for this NDA.

/S/ 3/23/00

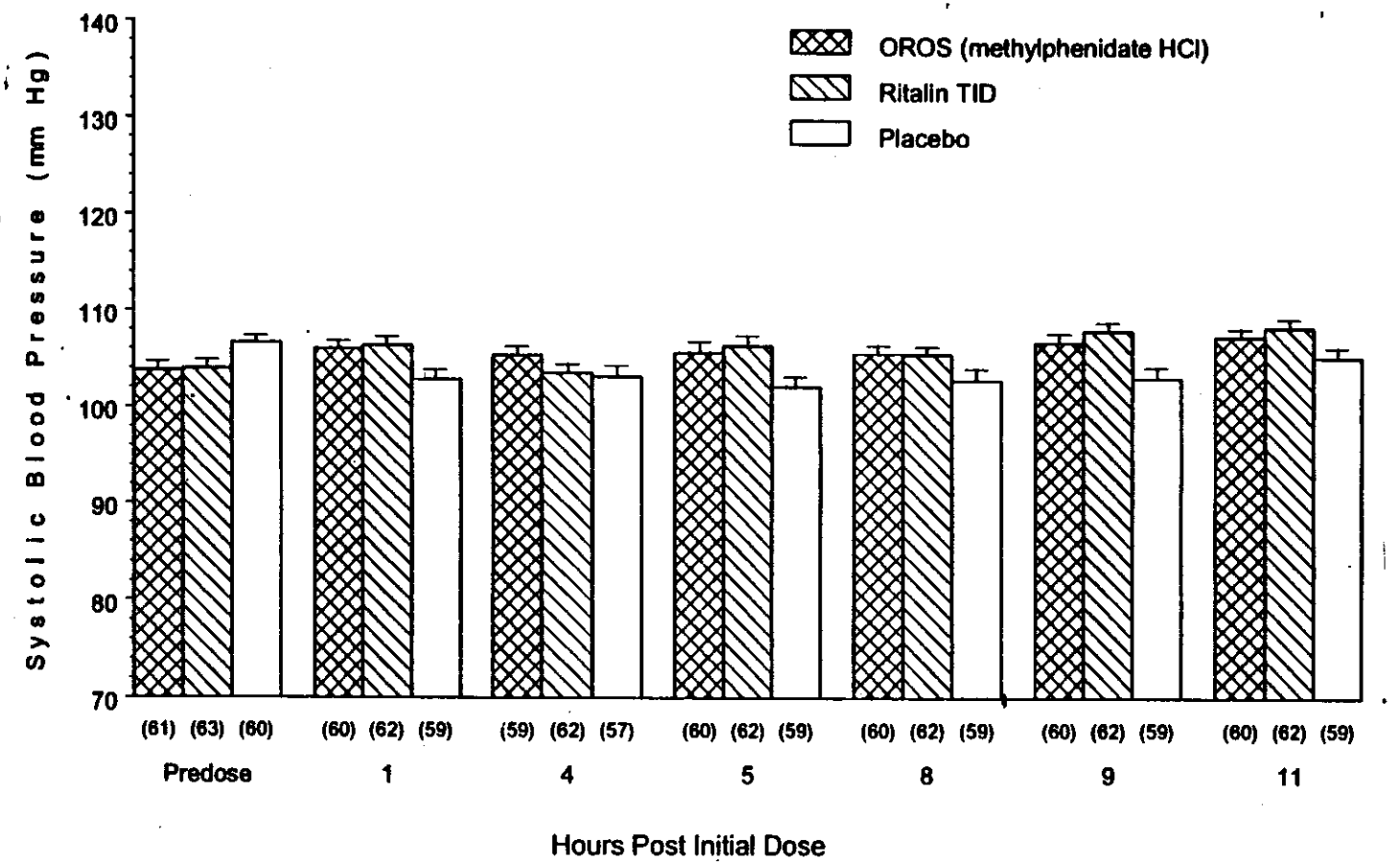
Andrew Mosholder, M.D.
Medical Officer, HFD-120

NDA 21-121
Div file
HFD-120 Laughren, Homonnay, Mosholder

4-27-00
I agree that the NDA is approvable. See memo to file for more detailed comments.

/S/
TL, PDP

FIGURE 11.2.2-1
Vital Signs During Laboratory School Days -
Mean(SEM) of Systolic Blood Pressure (mm Hg)
All Randomized Patients



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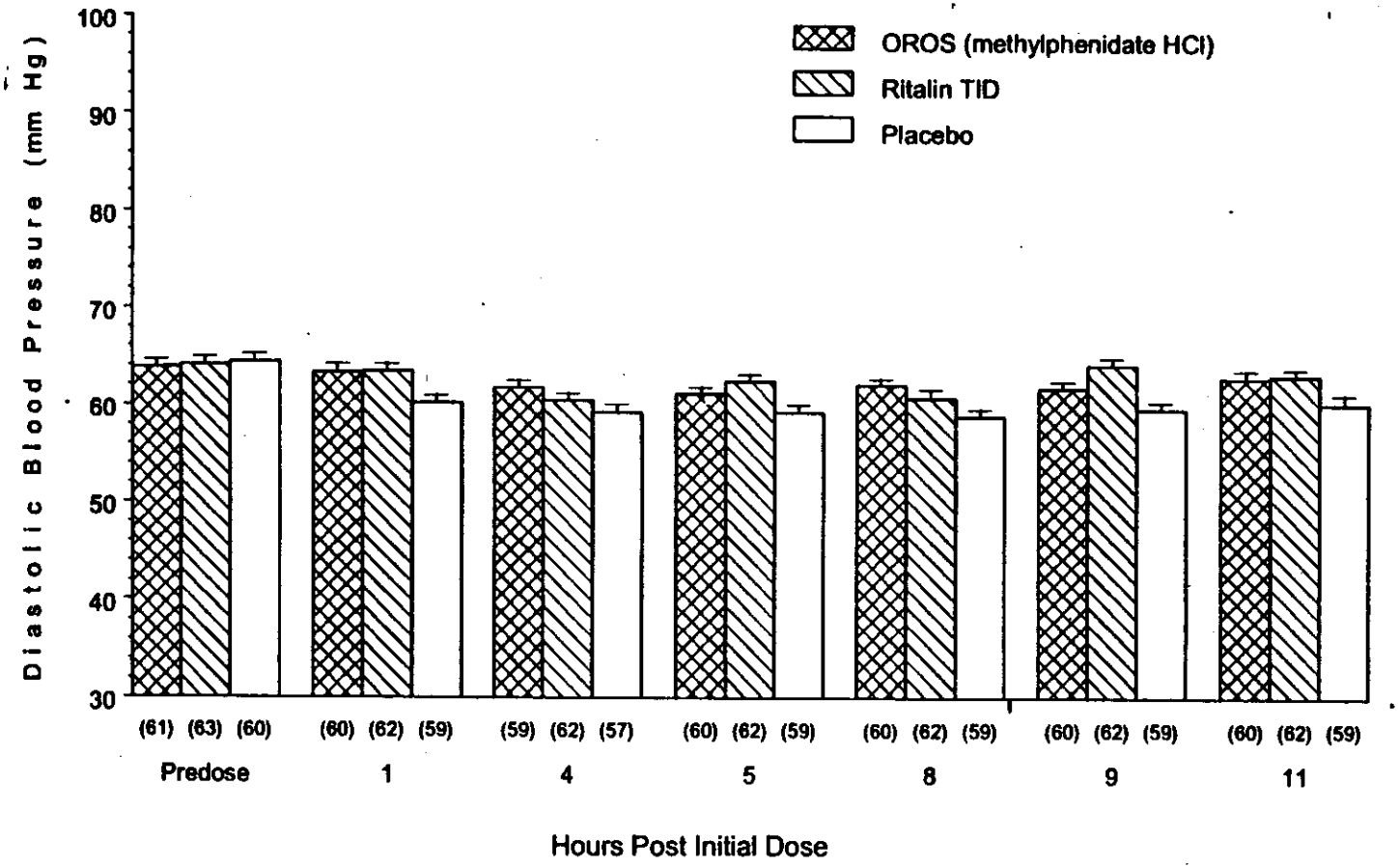
NDA 21-121 ATTACHMENT

FIGURE 11.2.2-2
Vital Signs During Laboratory School Days -
Mean(SEM) of Diastolic Blood Pressure (mm Hg)
All Randomized Patients



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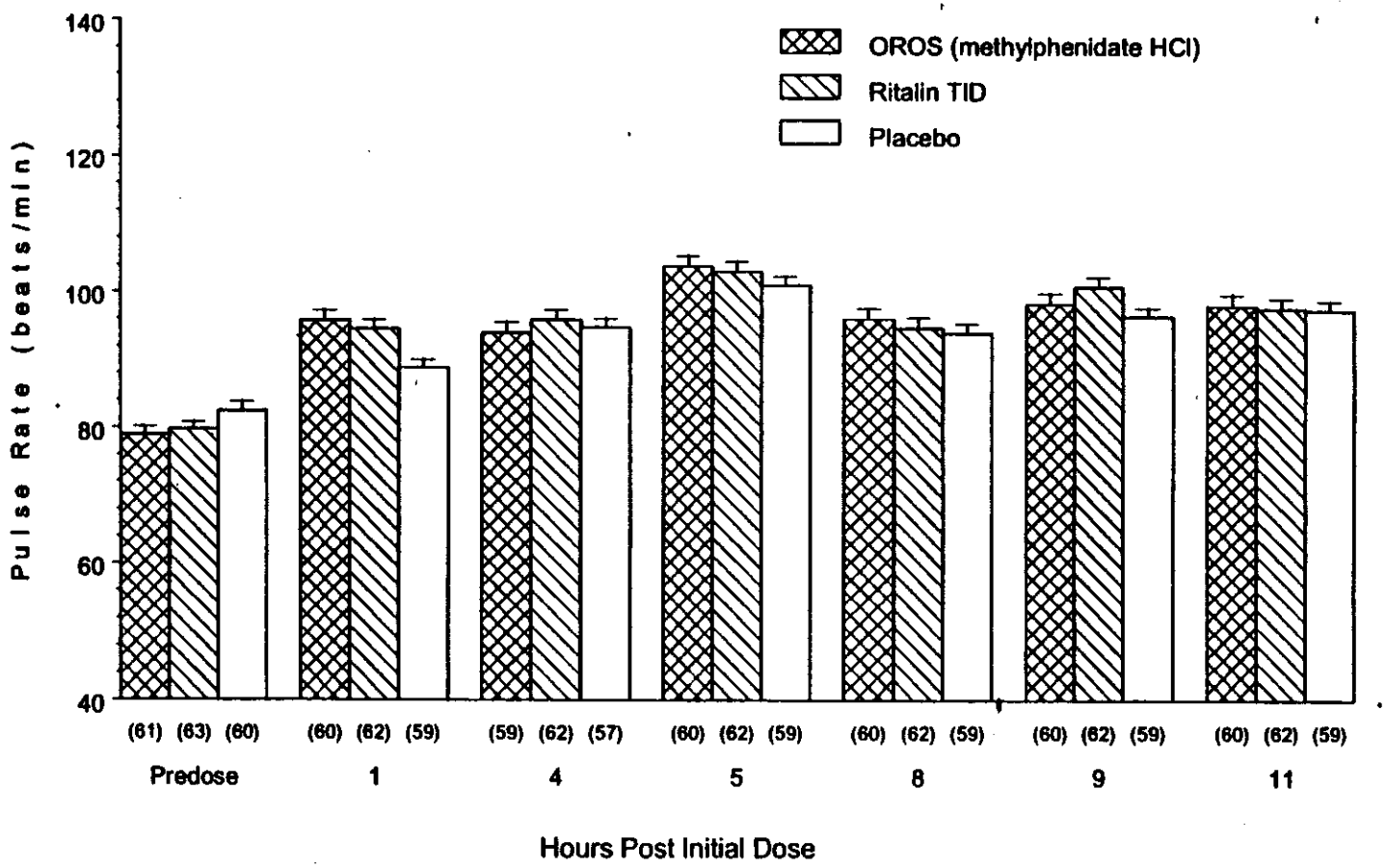
NDA 21-121 ATTACHMENT

FIGURE 11.2.2-3
Vital Signs During Laboratory School Days -
Mean(SEM) of Pulse Rate (beats/min)
All Randomized Patients



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NDA 21-121 ATTACHMENT

MEDICAL OFFICER'S CONSULT REVIEW

NDA 21-121
Concerta™ (Methylphenidate HCL)
Extended-Release Tablets
CII

COMPLETED MAR 9 9 200

MAR - 2 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S CONSULT REVIEW

NDA:	21-121
Sponsor:	ALZA Corporation 950 Page Mill Road PO Box 10950 Palo Alto, CA 94303
Drug:	Concerta™ (methylphenidate HCL)
Formulation:	OROS®
Route of Administration:	Oral
Therapeutic Category:	Mild central nervous system stimulant
Clinical Indication:	For the treatment of Attention Deficit Disorder (ADD)/Attention Deficit Hyperactivity Disorder (ADHD)
Date Assigned to Reviewer:	January 31, 2000
Date Draft Completed:	February 25, 2000
Material Submitted:	1. Request for consultation 2. Draft annotated physician insert December 1999 3. Introduction: Summary of safety data, information from ALZA Corp. regarding OROS® tablet sizes from Steve Ketchum, Ph.D July 12, 1999 4. Article Pharmaceut. Med. 3:35-43 (1988) 5. O [redacted] G [redacted] 6. Appendix I - Reports of GI Obstruction in the Literature (obtained prior to 1/27/53) 7. Appendix III - Summary of GITS products - GI obstruction 8. Appendix IV - Medical Officer's Review Dec. 7, 1990 for NDA 19-604, Volmax (Albuterol sulfate) 9. Addendum Dec. 18, 1990 Medical Officer's Review Nov. 28, 1990, Richard A. Nicklos, M.D. 10. Clinical Pharmacol. Ther. 39:501-509 (1986) 11. International Journal of Pharmaceutics 91:75-84 (1993)
Reviewer:	Raymond Joseph, M.D.

TABLE OF CONTENTS

I. Background/Introduction

Methylphenidate hydrochloride is a mild central nervous system stimulant. The proposed use for OROS® is in the treatment of Attention Deficit/Hyperactivity Disorder (ADHD)/Attention Deficit Disorder (ADD) in patients with combined, predominantly inattentive type, or predominantly hyperactive impulsive type ADHD/ADD. OROS® is proposed for use as an integral part of a treatment program for ADHD/ADD that typically includes additional therapies (psychological, educational, and social). Initially OROS® is planned to be marketed in two dosage strengths, 18 mg and 36 mg. Taken once daily, each tablet is designed to provide a therapeutic effect for approximately 12 hours.

OROS® looks like a conventional tablet. An osmotically active drug core is surrounded with a semipermeable membrane. This is encapsulated by an immediate-release drug overcoat, a color overcoat and a clear overcoat. The core contains three layers: two layers with the drug and a push layer containing pharmacologically inert (but osmotically active) **polymer excipients**. There is a laser-drilled orifice in the semipermeable membrane. In the gut the drug overcoat is expected todissolve within one hour, providing an immediate release of the active principle, methylphenidate. After dissolution of the overcoat, water is imbibed through the semipermeable membrane into the tablet core. As the polymer excipients expand, methylphenidate is released through the orifice in a uniquely patterned rate designed to provide a pharmacological effect for approximately 12 h. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the feces as an insoluble shell. This is the Push-Pull (P/P) system.

The 18-mg OROS® contains 4 mg in overcoat and 14 mg in the core. The 36 mg OROS® tablet contains 8 mg in the overcoat and 28 mg in the core.

II. Reason for Consultation

The rationale for the consultation to HFD-180 is to address the risks of adverse G.I. reactions such as **obstruction** and **bezoar formation**, which have been reported with other OROS® formulations. Special attention to the size of the tablets and use in children ≤6 y was requested.

III. The Consult

A. There are currently seven (7) prescription OROS® products marketed in the United States.

1. Volmax™ (4 mg).
2. Ditropan™ XL (5, 10, 15 mg)
3. Minipress XL™ (3.6 + 6.0 mg)
4. Glucotrol XL® (5, 10 mg)
5. DynaCirc CR™ (5, 10 mg),
6. Procardia XL™ (30 mg)
7. Covera-HS™ (240 mg).

There are two types of OROS systems, EOP and P/P (like Concerta™). Both types result in non-deformable materials in the g.i. tract. Hence, a precautionary statement has been included in the Draft Annotated Physicians insert which states:

> **As with any other nondeformable material, caution should be used when administering Concerta™ to patients with preexisting severe gastrointestinal**

narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs in nondeformable controlled-release formulations."

B. 1) The most widely distributed of all OROS® products in the push-pull formulation is the calcium channel blocker **Procardia XL**).

2) **Volmax® (albuterol/salbutemol)** was introduced to the U.S. market in Sept. 1993. The incidence of gastrointestinal obstruction is approximately

3) **Efidac/24®** (pseudoephedrine HCL) and **Efidac/24** (chlor-pheniramine maleate) introduced to the US market in 1993 and 1994,

ion.

4) **Glucotrol-XL®** (glipizide) introduced in the United States in 1994

5) **Covera-HS™** (verapamil HCL) was introduced in June 1996

IV. Summary (Reviewer)

1) OROS® controlled-release dosage forms have been safely used worldwide in numerous marketed prescription and over-the-counter formulations for more than 20 years. This has provided a substantial body of clinical and commercial experience. The following table summarizes the market introductions of the various OROS® products. Approximate numbers of systems distributed are listed.

TABLE P
Marketing History of OROS® Products

Product	Market Introduction	Approximate Number of Systems Distributed
Acutrim® (phenyl-propanolamine HCl)	US 1983	
Acusystem C® (calcium ascorbate)	US 1987[b]	
Ditropan XL® (oxybutynin chloride)	US 199	
Meloros® (metoprolol fumarate)	UK 1988[b]	
Minipress XL® (prazosin HCl) [Alpress LP®]	France 1989	
Procardia XL® (nifedipine) [Adalat OROS, Adalat CR]	US 1989; ex-US in 25 countries, first in 1991	nly)
Volmax® (salbutamol sulfate) [ventolin CR]	ex-US in >75 countries, first in 1987; US 1993	
Efidac/24® (pseudoephedrine HCl)	US 1993	
Efidac/24® (chlor-pheniramine maleate)	US 1995	
Glucotrol XL® (glipizide)	US 1994	
Covera-HS (verapamil HCl)	US 1996	
Dynacirc® (isradipine HCl)	US 1997	

[a] Data current as of December 1993.
[b] No longer marketed for economic reasons.
[c] Data current as of October 1996.
[d] Data current as of September 1996.
US sale nber 1997. xd data for
[f] Data current through May 1999.

OROS® is designed to deliver methylphenidate HCL in a controlled pattern although, as already mentioned, OROS® is similar in appearance to a conventional tablet.

2) The data related to the use of OROS® products in Pediatric/Adolescent populations derive from ALZA's safety database of spontaneously reported adverse events for OROS (pseudoephedrine HCL) marketed as Efidac/24® (pseudoephedrine HCL) 240 mg and Pseudofed® 24 hour. From 1994 to May 1999 there were 18 reports of serious adverse events in patients 18 years of age or younger. One report described an accidental overdose while all others involved known adverse events associated with pseudoephedrine administration.

Another OROS® product used in the pediatric/adolescent populations is Volmax (salbutamol sulfate). Two reports (previously mentioned) involved complete G.I. obstruction in patients with some degree of pre-existing obstruction. There were no reports of overt gastrointestinal bleeding or local gastrointestinal irritation.

V. Conclusions/Recommendations for Regulatory Action

In this NDA (21-121) the sponsor requests the marketing of Concerta™ (methylphenidate HCL) in the treatment of Attention Deficit Hyperactivity Disorder (ADHO)/Attention Deficit Disorder (ADD) in patients with combined type, predominantly inattentive type, or predominantly hyperactive-impulsive type AOHO/ADD.

After an assessment of the information provided it is concluded that the potential for g.i. obstruction and bezoar formation with OROS products does exist but that the incidence of the events may be quite rare.

However, a lingering concern is the large size of the tablets. Below is a table listing physicial characteristics, including size in inches, of prescription OROS products currently marketed in the United States.

OROS® Product	Shape	Diameter (Inches)	Thickness (inches)
OROS® (methylphenidate HCl) 18 mg	Caplet	0.21	0.47 (length)
Volmax® 4 mg	Pentagonal	0.22	0.09
OROS® (methylphenidate HCl) 36 mg	Caplet	0.27	0.59 (length)
Ditropan® XL 5 mg	Round	0.28	0.16
Ditropan® XL 10 mg	Round	0.28	0.16
Ditropan® XL 15 mg	Round	0.28	0.16
Minipress XL® 2.5 mg	Round	0.28	0.16
Glucotrol XL® 5 mg	Round	0.31	0.16
DynaCirc CR® 5 mg	Round	0.31	0.17
Procardia XL® 30 mg	Round	0.34	0.18
Minipress XL® 5 mg	Round	0.34	0.19
DynaCirc CR® 10 mg	Round	0.38	0.21
Glucotrol XL® 10 mg	Round	0.38	0.21
Covera-HS™ 180 mg	Round	0.41	0.23
Covera-HS™ 240 mg	Round	0.44	0.23

The OROS products, both the 18 mg and the 36 mg caplets are significantly larger than Volmax 4 mg, the product most widely used among adolescents.

Since all of the previous cases of g.i. obstruction have involved patients with pre-existing narrowing of the gastrointestinal lumen, this consultant feels the drug should be contraindicated in the following types of patients:

1)
2)
3)
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5)
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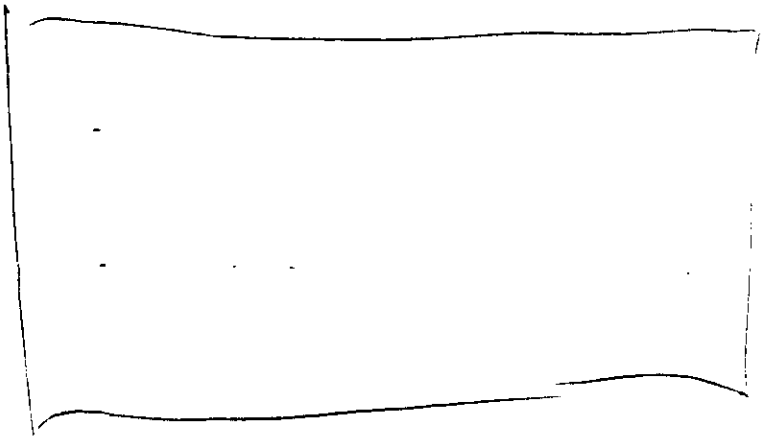
7) t



In addition, due to the lack of long term exposure to a caplet of this size in a pediatric population a precautionary note should be added to the **PRECAUTIONS SECTION** of the labeling. With regard for the size of the caplet ***"Due to the large size of the caplet, special care should be taken when using this product in younger children (6-11 years of age).***

Careful and continuous post-marketing monitoring is also recommended.

/S/
Raymond Joseph, M.D.

cc:
NDA 21-121
HFD-180/LTalarico
HFD-180/SAurecchia
HFD-180/HGallo-Torres
HFD-180/RJoseph
HFD-181/Consult File
HFD-120/A. Mosholder
f/t 3/1/00 jgw
N/21121002.0RJ

/S/ /S/ M.D., Ph.D.

Pharmaceut. Med. (1988), 3, 35–43

Fatal Gastrointestinal Damage Associated with the Use of Osmotic Mini Pump Indomethacin (Osmosin)

J. L. Bem, R. D. Mann & R. Coulson

Committee on Safety of Medicines, Market Towers, 1 Nine Elms Lane, London SW8 5NQ, U.K.

Introduction

The development of Osmosin represented an attempt to introduce a unique pharmacokinetic approach into the clinical use of a non-steroidal anti-inflammatory agent (NSAID). The principle of the osmotic minipump marketed by Alza Corporation offered a potentially attractive drug delivery system capable of achieving an effective, steady level of a drug in the plasma for 10–12 h.[1] The early efficacy and safety data for this formulation of indomethacin were encouraging.[2]

Osmosin was marketed in the UK at the beginning of 1983.[3] In July 1983 a surgeon informed the Committee on Safety of Medicines (CSM) of two cases of intestinal perforation distal to the duodenum in patients who were treated with Osmosin.[4] The perforations were pathologically distinctive, a well defined ulcer with 'punched out' edges located in the small bowel, where such ulcers are extremely rare.

The number of suspected adverse reactions associated with the use of Osmosin and reported to the CSM was significant and represented a high rate of reporting even for a recently introduced product;[5] furthermore a number of the reactions were of a serious nature. The adverse effects of Osmosin were especially prominent in the gastrointestinal system. A total of 25 non-steroidal anti-inflammatory drugs were reviewed in the *CSM Update* of May 1986;[3] with these drugs 58% of the reported serious suspected adverse reactions were gastrointestinal in nature. In the case of Osmosin 95% of all reported serious suspected reactions were gastrointestinal. A similar difference was noted in respect of deaths: all suspected adverse reaction deaths associated with Osmosin were due to gastrointestinal lesions, whereas only 72% of such deaths associated with the use of indomethacin and, for all 25 NSAIDs, only 40% of deaths due to suspected adverse reactions, were gastrointestinal in nature.[3]

Osmosin was removed from the market in September 1983. The circumstances of its removal, the prescription data, the number of adverse reactions reported and the duration of the marketing period have been reviewed elsewhere.[6]

The purpose of this paper is to review the Osmosin safety data and, in particular, the problem of intestinal perforation.

Number of Pages Redacted 7

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Confidential,
Commercial Information

Literature